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DISEASES OF THE DIGESTIVE SYSTEM

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AFFECTIONATELY DEDICATED TO MY BROTHER

DR. MILTON M. PORTIS

MY FIRST TEACHER OF GASTROENTEROLOGY

PREFACE TO THE SECOND EDITION

Many changes have occurred in the field of gastroenterology. The short space of three years has brought forth much new material. The impact of the war, the opportunity for studying at close hand the beginning of changes in young adults, which later may lead to sustained and persistent pathologic physiology, is evident to any student in this field. The large number of psychosomatic problems among members of the armed forces, particularly as they affect the gastrointestinal tract, form a fertile field for future study. Already filtering back to civilian life, discharged members of our fighting forces demand more thorough understanding of the underlying problems. Therefore, the effect of emotional stimuli on the gastrointestinal tract has opened up a new field for the gastroenterologist. This is one of the many new problems which need greater clarification. While no complete answer can be given to it at this time, an attempt at more complete understanding has been made by contributors. The psychodynamics and psychogenesis of this pathologic physiology, presenting bizarre clinical pictures which previously have been erroneously classified under nervous indigestion and a host of similar inadequate diagnoses, pose problems for further study.

Each contributor was asked, so far as possible, in connection with his special subject, to discuss this aspect. The chapter by Alexander has been enlarged to try to meet this need from the standpoint of the psychiatrist. I hope the reader will be impressed by the sincere attempt to lay some solid foundation for further exploration.

Other contributors have brought their respective chapters up to date, emphasizing the new experimental work and clinical information so far as it affects their contributions. Many of the authors are serving in the armed forces. They have revised their chapters as far as was humanly possible, considering the tremendous burdens placed upon them by the war. For their hearty coöperation I am especially grateful.

The reader will also note that the chapters have been rearranged especially for students and teachers in this field. The physiology of each organ is now taken up immediately before its clinical discussion, in order to lay a more solid foundation for the understanding of diseases of the gastrointestinal tract. Discussion of gastrointestinal complaints of extra-abdominal origin has been placed at the end. This is particularly adapted for students, because it is my belief that with a complete understanding of the fundamental problems of digestive disturbances they will be able better to evaluate these manifestations and arrive at a more accurate diagnosis of the patient's complaints.

Finally, I am deeply grateful for the cordial reception of the first edition and the generous comments of the reviewers. These have stimulated me to undertake this second edition.

Sidney A. Portis.

104 S. Michigan Ave., Chicago, Illinois.

PREFACE TO THE FIRST EDITION

THE field of gastroenterology has developed rapidly in the last twenty years. Many new diseases and diagnostic aids have opened new avenues of approach. The time-honored method of teaching the subject as diseases of the esophagus, stomach, gallbladder and colon, based on necropsy evidence, is somewhat archaic. The modern gastroenterologist must be thoroughly trained in the laboratory and have a broad general clinical experience in all branches of internal medicine. Further, he must be able to interpret the laboratory evidence and give to it its proper clinical significance. Incipient symptoms must be approached critically and functional factors simulating organic disease must be carefully evaluated. Above all, the gastroenterologist must remember that he is a clinician and will frequently have to reach a positive diagnosis in the absence of corroborative laboratory results. However, with the increasing development of laboratory and roentgenologic aids, this difficulty, fortunately, is rapidly disappearing. The student and practitioner must be enlightened regarding the many conditions and diseases with gastrointestinal symptoms in which pathologic changes in the gastrointestinal tract *per se* do not exist.

I have frequently been asked by students where they might find a book or books on the subjects herein discussed. Unfortunately, at present I cannot recommend any other one book which will meet the demands of the student. Nor is there any contribution in a single volume that will meet all the needs of the general practitioner. The development of modern scientific gastroenterology has been so rapid that it is difficult for any one person to present the subject in its entirety. It was therefore thought desirable that a book be developed which would present the views of physicians who have made a special study in some branch of gastroenterology and whose clinical experience is broad enough to justify a contribution on their subject. I have attempted to select contributors with this thought in mind. For the most part, the contributions have been left in their original state, because it has been my desire to maintain the individuality of the authors.

I am deeply grateful to them for their cordial response, their willingness to undertake their respective chapters and their conscientiousness in presenting their particular subjects.

Some diseases and some fields of gastroenterology necessarily had to be omitted because of the limitations of space. The reader will have a much broader knowledge of the whole field of gastroenterology after reading these chapters. The contributors have been urged to put particular stress on the contributory causes of gastrointestinal symptoms which form important links in arriving at a final diagnosis of the patient's complaints. The contributions on the history of gastrointestinal disease, the anatomy and the normal and abnormal physiology lay a splendid foundation for a clear understanding of diseases of the digestive system.

As a teacher, I hope this book meets to some extent the demands of both the student and the practitioner.

I am deeply grateful to Dr. Morris Fishbein for his critical advice and helpful suggestions, and to my publishers for their splendid coöperation.

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Diseases of the Digestive System

PART I

Introduction

CHAPTER I

THE HISTORY OF OUR KNOWLEDGE OF GASTRO-INTESTINAL DISEASE

The history of diseases of the gastrointestinal tract begins with the dawn of history, although only a few pages of its ancient history were written with sufficient clarity to be legible today. Diseases of the gastrointestinal tract were mentioned in these pages, but the clinical picture was often described with such haziness as to be unrecognizable.

The Papyros Ebers, compiled about 1550 B.C., described some cases of what Ebbell interpreted as "weak digestion, constipation with meteorism and rumbling," "hemorrhage of the stomach," "dilatatio ventriculi" and possibly "appendicitis." But these descriptions were by no means so clear as the unmistakable descriptions of suffering from roundworm (*Ascaris lumbricoides*), tapeworm (*Taenia*), bubonic plague, malaria and tuberculosis.

The ancient Greek physicians, who saw clearly, reasoned cogently and wrote succinctly, have left few, if any, accounts of gastrointestinal disease (excepting those of infectious origin) which can be recognized from the description alone. Hippocrates (460–370 B.C.), as Garrison remarked, left us "clinical pictures of phthisis, puerperal septicemia, epilepsy, epidemic parotitis, the quotidian, tertian, and quartan varieties of remittent fever" that "might, with a few changes and additions, take their place in any modern text-book." However, he devoted little attention to the stomach and intestines. He mentioned wounds of the stomach and noted that cold drinks and warm food are most agreeable to the stomach. His remarks about the intestine were brief. He observed that the intestine does not unite after being severed and remarked that wounds of the intestine are serious and that the intestine appears ulcerated in dysentery. He saw patients with an undoubted intestinal obstruction, stating that "whatever they drank or ate they vomited and finally vomited fecal material." Hippocrates also described diseases of the liver. One patient, the currier of Cleotimus, who suffered from persistent diarrhea and in whom there presently developed a phlegmonous tumor of the liver from which he died, probably suffered from amebic dysentery with a liver abscess. He described hydrops arising from a liver which was indurated and swollen, which may have been cirrhosis of the liver with ascites. Icterus was well known to Hippocrates, and he made frequent reference to it.

Aretaeus the Cappadocian, who lived in either the second or the third century of the Christian era, is much appreciated by modern readers. He left masterful accounts of diabetes, diphtheria, epilepsy, tetanus and pleurisy. His description of gastrointestinal diseases included, however, nothing that was not described by Hippocrates, although he left excellent descriptions of cholera and of ileus.

Galen (131–201 A.D.), physician to Marcus Aurelius and one of the earliest physiologists, described tumors and ulcers of the esophagus and mentioned inflammations, abscesses and tumors of the stomach, as well as tumors of the liver, hardening of the liver and ascites due to hepatic disease. His ideas of the circulation of the blood, of the processes of digestion and of the functions of the stomach and liver were, however, erroneous, and these fundamental misconceptions permeate all his discussions of diseases of the gastrointestinal tract. Most of his descriptions of gastrointestinal diseases are shrouded in a maze of philosophic and physiologic theory. It is, however, perhaps noteworthy that he pointed out clearly the differential diagnosis of pains in the right hypochondrium, noting that those due to disease of the lung were accompanied with cough and bloody sputum, while these signs were absent in disease of the liver.

Physicians in the centuries following Galen, such as Alexander of Tralles (525–605) and Paul of Aegina (625–690), discussed diseases of the gastrointestinal tract but presented nothing new of historical importance. Garrison remarked with truth that

> Up to the time of Vesalius, European medicine was one vast *argumentum ad hominem*, in which everything relating to anatomy and physiology, as well as disease, was referred back to Galen as a final authority, from whom there could be no appeal. After his death, European medicine remained at a dead level for nearly fourteen centuries.

This statement, the accuracy of which is undisputed, has often been quoted in condemnation of Galen. The blame, however, should be cast on his successors and not on Galen himself, for with all his errors, he made many discoveries of the greatest importance, and as an indefatigable experimenter, he deserves the title of the father of experimental physiology.

Medicine was finally aroused from the long lethargy into which it fell after the death of Galen by the establishment of anatomy and pathologic anatomy as sciences worthy of the name. Even before Vesalius taught that human anatomy should be learned from human bodies and not from the books of Galen, a Florentine physician, Antonius Benivenius, learned that incomparable knowledge was to be acquired by performing autopsies on his patients and attempting to explain their symptoms by the postmortem findings. Benivenius' work *De abditis nonnullis ac mirandis morborum et sanationum causis liber* (Book of Some Hidden and Remarkable Causes of Diseases and Their Cure), published in 1507, five years after his death, described ulcers of the intestines, carcinoma of the stomach and stones in the gallbladder. "With him for the first time," Prof. Bindo de Vecchi remarked, "the physician considers the problems of the causes of disease and death, and seeks their explanation in the dead body. No one had thought thus before him, and after him the physicians of the entire world should have had the same thought."

However, two hundred and sixty-six years elapsed before a fellow countryman, Giovanni Battista Morgagni (Fig. 1), when eighty years of age, in 1761 published his famous *De sedibus et causis morborum* (The Seats and Causes of Disease), a work in which he founded the modern science of pathologic anatomy. In this work, which was composed in the spirit of his predecessor Benivenius, Morgagni remarked: "Those who have dissected or inspected many bodies, have at least learned to doubt; when others, who are ignorant of anatomy and do not take the trouble to attend to it, are in no doubt at all." This monumental treatise described ulcers of the stomach and intestine, phlegmonous gastritis, carcinoma of the stomach and esophagus, tumors of the liver, acute yellow atrophy, gallstones and cirrhosis of the liver.

HIC EST VT PERHIBENT DOCTORVM CORDA VIRORVM PRIMVS IN HUMANI CORPORIS HISTORIA
JOANNES BAPTISTA MORGAGNVS
natus Foroliuii die 25 Februarii anno 1682
in Patavino Gymnasio e Primaria Sede
Anatomen adhuc docebat anno 1762

FIG. 1.—Giovanni Battista Morgagni.

Even before the publication of Morgagni's work, in 1685 John Brown, surgeon to St. Thomas Hospital in London, published a description of cirrhosis of the liver, illustrated by a somewhat schematic drawing (Fig. 2). Matthew Baillie's *Morbid Anatomy*, published in 1812, contained an excellent illustration of the same condition, although it remained for Laënnec, in 1826, "to designate it with the name of cirrhosis because of its color."

Jean Cruveilhier, who desired to be a priest but was compelled by his domineering father to become a physician instead, contributed so much to the advancement of medical science that we cannot but be grateful to his domineering father. He was appointed professor of descriptive anatomy at Paris in 1825 and in 1836 became the occupant of the newly created chair of pathologic anatomy. He held this position for thirty years and published, during the years 1830 to 1842, his justly celebrated *Anatomie pathologique du corps humain.* This work was a vast storehouse of pathologic anatomy and from the artistic standpoint was the most beautiful and magnificent atlas of pathology ever published. In this atlas, Cruveilhier described and illustrated superbly a great variety of pathologic lesions of the intestinal tract. Among these were several gastric ulcers (Fig. 3)—still called by the French "la maladie de Cruveilhier."

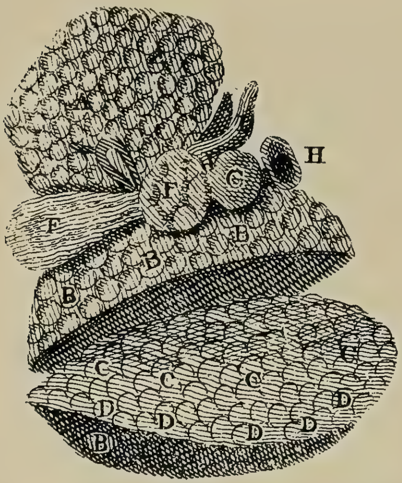

FIG. 2.—John Brown's drawing of cirrhosis of the liver.

The importance of this disease was stressed by Kussmaul in a chapter of his *Jugenderinnerungen eines alten Arztes*, in which he described the notes taken by his father in Schönlein's clinic in Würzburg during 1819 and 1820. Kussmaul wrote: "The diagnosis of lienitis or inflammation of the spleen, which we seldom make today, appears often in his notebook. Schönlein explained gastric hemorrhage usually by lienitis, since it had not yet been proved by the anatomists Cruveilhier and Rokitansky that it usually comes from ulcers of the stomach."

Karl Rokitansky (1804–1878), one of the corner stones of the new school of medicine in Vienna, was undoubtedly one of the greatest masters of gross pathology who ever lived. As director of the Institute of Pathological Anatomy, he is said to have performed more than 30,000 autopsies, in the course of which he naturally saw numerous examples of diseases of the digestive organs, which he described in his reports. Rokitansky, the master of pathology for a full generation, abdicated when his younger rival, Rudolf Virchow (1821–1902), published, in 1856, his epochal *Cellularpathologie*, a book which marks the foundation of modern pathology and the introduction of microscopic tissue diagnosis in medicine. Virchow, during his remarkably productive life, studied a great variety of pathologic lesions in the esophagus, stomach, intestines, liver and pancreas. His studies, with the classification of lesions from their microscopic structure, represent in the main the final chapter in the morphologic history of disease.

The study of the processes of digestion began with the teachings of that erratic genius Philippus Aureolus Theophrastus Bombastus von Hohenheim, better known as Paracelsus (1493–1541). Paracelsus, regarded with suspicion by many of the clergy in his day, is worshipped as a saint today by the peasants, who pray at his tomb in St. Sebastian's Church in Salzburg; treated as a charlatan by his contemporaries, he is regarded by many competent historians as the father of chemical thinking in the domain of medicine. Jan Baptista van Helmont (1577–1644) was born after the death of Paracelsus but regarded himself as his disciple. Paracelsus was the only one of his predecessors with whom he regarded himself as mentally akin. Van Helmont, originally a friar of the Capuchin order, studied medicine and then traveled widely, just as Paracelsus had done. Van Helmont elaborated an extremely fantastic theory of health and disease, stressing greatly the influence of "ferments" on health and disease. The changes that appeared in various organs in disease were, he maintained, chemical processes. Bizarre as many of van Helmont's ideas were, his general influence on medicine was beneficial, since he directed the attention of physicians to organs and not to humors as the seat of disease and stressed the importance of chemical changes.

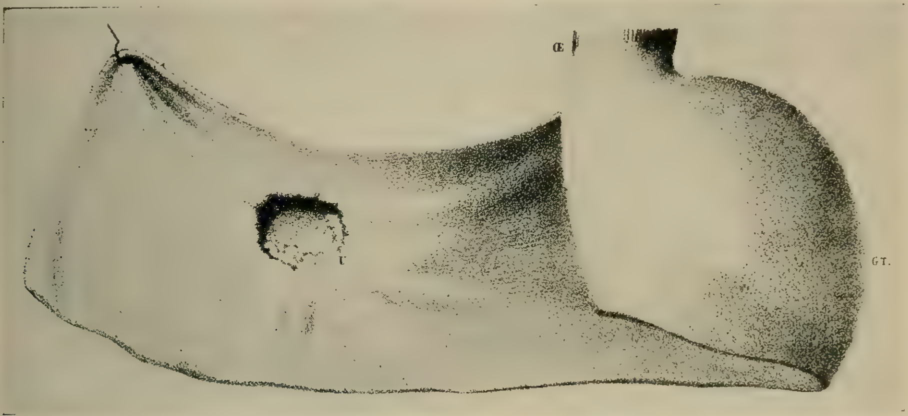

Fig. 3.—Ulcer of the stomach, from Cruveilhier's *Anatomie pathologique du corps humain.*

The introduction of chemistry into medicine gave rise to the iatrochemical school, whose most distinguished exponent was Franz de le Boë (1614–1672), better known by his latinized name of Franciscus Sylvius. Sylvius laid great stress on the chemical fermentations in the body, on acids and alkalis, on the acidity of the body juices and on the necessity of preserving a proper balance between acid and alkali in the stomach, bile and intestines. The stimulus of these ideas led Regner de Graaf (1641–1673), a pupil of Sylvius, to study the physiology of the pancreas. His success in isolating and studying the properties of pancreatic juice remains one of the classic discoveries of physiology, just as his drawing of this experiment (Fig. 4) is one of the most interesting illustrations in the annals of medical history.

A further extension of this interest in physiologic experimentation is seen in the work of René Antoine de Réaumur (1683–1757), a distinguished French scientist. Réaumur invented the thermometer which bears his name, wrote a six volume treatise on insects which remains a classic and made important contributions to the sciences of metallurgy, physics and mathematics. Of all his numerous investigations in various fields, his studies of digestion are perhaps the most interesting. Réaumur was the owner of a pet kite, a bird of prey which ejects from its stomach articles of food that are unpalatable. He fed the kite metal tubes containing meat, starch and bone and provided with a grating to prevent escape of their contents. He found the contents of the tubes after ejection to be partially digested and to show no sign of putrefaction. He next fed the kite metal tubes containing pieces of sponge and after regurgitation found that gastric juice could be squeezed out of the sponge. He collected a quantity of gastric juice by this method and studied its properties. He found that it turned blue litmus paper red, that when bits of meat were placed in it they were partially digested and that no putrefaction took place. He decided that gastric juice has a solvent power and that gastric digestion is neither trituration nor putrefaction.

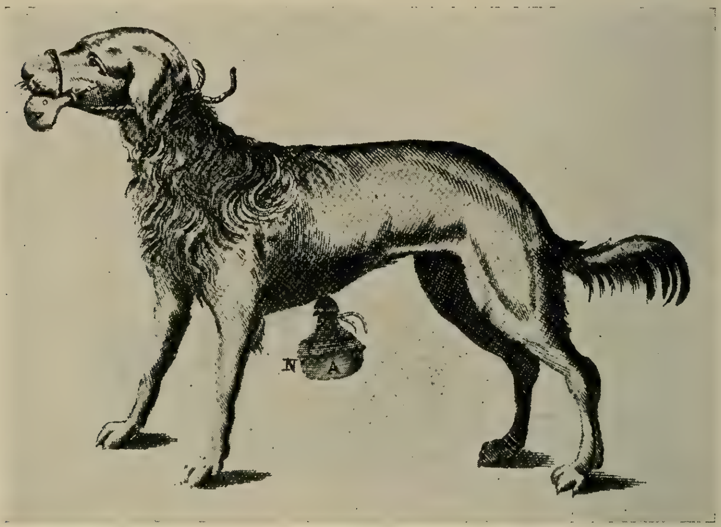

Fig. 4.—Graaf's drawing of a dog with a parotid and pancreatic fistula.

Réaumur's work was carried further by Lazaro Spallanzani (1729–1799) (Fig. 5), who became a priest at twenty-six but for the remaining forty-four years of his life devoted much of his time to matters not related intimately to theology and who "stands a dominant figure as a man of letters, as a naturalist, physicist, chemist, geologist, volcanologist and physiologist" (Franchini). Spallanzani first attracted the attention of the scientific world by his investigations on infusoria and further established his reputation by his accurate and correct observations on spontaneous generation, but is best remembered by posterity for his work on digestion.

Spallanzani employed largely the methods of study introduced by Réaumur. He used metal tubes closed by a grating at either end and experimented on many different kinds of animals—fishes, frogs, newts, serpents, birds of various kinds, sheep, oxen, horses, cats and dogs—and finally on himself. He fed animals pieces of meat attached to threads or wires and withdrew them after varying periods. He himself swallowed small linen bags and perforated tubes containing meat and bread, which he examined after passage *per anum*. He obtained gastric juice from animals by making them swallow tubes containing sponges and obtained gastric juice from himself by vomiting before breakfast, when his stomach was empty. With the gastric juice Spallanzani carried on numerous experiments, in which he proved it acts on food as well *in vitro* as in the stomach.

While Spallanzani was carrying out his experiments on digestion in Italy, the famous John Hunter (1728–1793) was working on the same subject in London. Spallanzani's experiments aroused the ire of Hunter, who complained that the former worker was not an anatomist and that "like all mere experiment-makers, he is not satisfied even with those which are clear and decisive, but multiplies them most unnecessarily." Hunter continued to expound his ideas regarding the manner in which experiments should be conducted and added, "if Spallanzani had employed half his time in this way . . . he had employed his time much better than in making experiments without end."

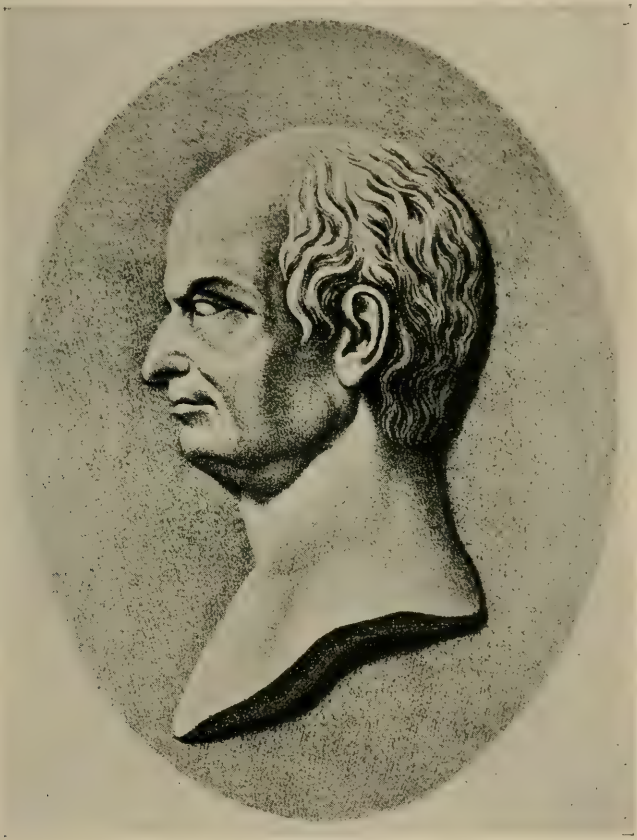

Fig. 5.—Lazaro Spallanzani.

Hunter, who was firmly imbued with the idea of a "vital principle," was much annoyed by Spallanzani, who was eminently free from vitalistic tendencies as well as from theorizing on physiologic topics. Spallanzani answered Hunter's rude and sarcastic criticism in a dignified and scientific manner which left no further retort possible.

William Beaumont has summarized in a few terse sentences the contribution of Spallanzani to the knowledge of digestion: "It would be a waste of time to attempt to refute the doctrines of the older writers on this subject. Suffice it to say, that the theories of *Concoction, Putrefaction, Trituration, Fermentation* and *Maceration,* have been prostrated in the dust before the lights of science, and the deductions of experiment. It was reserved for Spallanzani to overthrow all these unfounded hypotheses, and to erect upon their ruins a theory which will stand the test of scientific examination and experiment. He established a theory of *chemical solution* and taught that chymification was owing to the solvent action of a fluid, secreted by the stomach, and operating as a true menstruum of alimentary substances. To this fluid he gave the name of *gastric juice*."

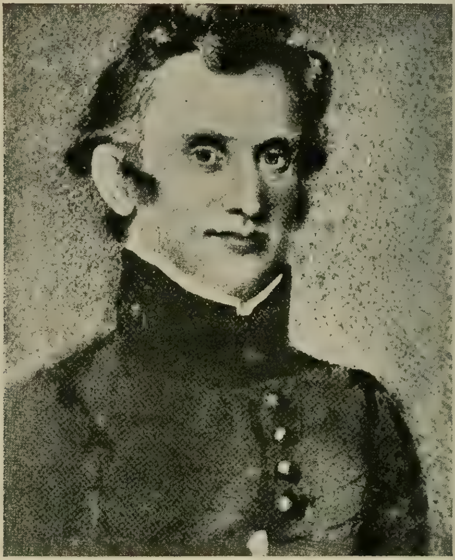

Fig. 6.—William Beaumont.

Spallanzani asked his colleague and friend Scopoli, professor of chemistry at the University of Pavia, to examine the gastric juice he had obtained from crows. Scopoli reported that it contained water, a saponaceous and gelatinous animal substance, sal ammoniac and an earthly matter. Spallanzani then erroneously concluded that gastric juice contained no acid, although he was puzzled as to why it should curdle milk. John Hunter was, however, correct in writing, "I constantly found there was an acid, though not a strong one, in the juices contained in that viscus in a natural state." He later invalidated this positive assertion a bit by writing, "It is only formed occasionally. Whether the stomach has the power of immediately secreting this acid or first secretes a sugar which afterwards becomes acid, is not easily ascertained."

The controversy regarding the acidity of the gastric juice was finally settled by William Prout, the first English physiologic chemist, who proved in 1824 that the normal gastric juice contains free hydrochloric acid. This important discovery was confirmed two years later by Friedrich Tiedemann and Leopold Gmelin in their classic monograph *Die Verdauung nach Versuchen.*

William Beaumont (1785–1853) (Fig. 6), who quoted Spallanzani with such approval, added one of the most important chapters in the history of digestion and, as Garrison remarked, "was the first to study digestion and the movements of the stomach *in situ* (1825)." Beaumont's story has become a classic in the history of medicine. A surgeon in the United States Army, Beaumont in 1822, while stationed in the primeval forest of northern Michigan, was called to attend Alexis St. Martin, a French Canadian voyageur who had been wounded by the accidental discharge of a musket. "The charge, consisting of powder and buck shot, was received in his left side, he being at a distance of not more than one yard from the muzzle of the gun," and perforated his stomach. The wound in his side healed but left a gastric fistula, thus affording Beaumont an opportunity of studying gastric digestion *in situ* (Fig. 7). His experiments were begun in Michillimackinac, Michigan Territory, in 1825, continued at Fort Niagara, New York, at Fort Crawford, Wisconsin, at Plattsburg Barracks, New York, and at Washington, D. C., and completed in 1833, after he had succeeded in bringing his patient several thousand miles to carry out his studies.

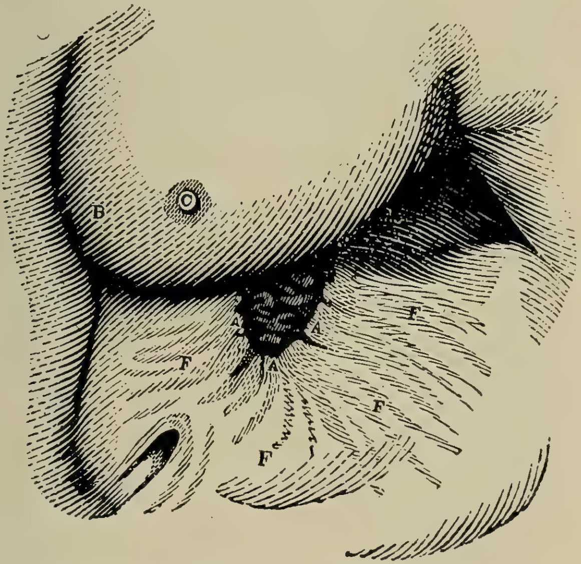

FIG. 7.—Gastric fistula of Alexis St. Martin, from Beaumont's *Experiments and Observations on the Gastric Juice and the Physiology of Digestion.*

Beaumont observed the normal appearance of the gastric mucosa, noted that gastric juice is secreted only when food is present and that irritation of the gastric mucosa produces redness but only a limited amount of secretion. His studies on the relative digestibility of various foodstuffs mark the foundation of modern dietetics. Beaumont found that while gastric juice outside the body digested beefsteak perfectly, an aqueous solution of hydrochloric and acetic acids failed to do so, and concluded that the gastric juice "contains free *Muriatic Acid* and some other active *chemical* principles." The other active principle, pepsin, was isolated in 1835 by Theodor Schwann, who showed it converted nondiffusible albumins into peptones.

"Beaumont's observations," Fulton noted, "illustrate the enormous contribution which may come from painstaking clinical observation and those who read his little book must inevitably feel the inspiration of his great example." Beaumont's book is a classic in physiology.

The stomach tube, which has played an important role in the treatment and diagnosis of gastric diseases, has a history which harks back to the days of antiquity. Its forerunner was the *pinna*, or "vomiting feather," which the gluttonous Romans used at their feasts, employing it after each course to make room for the one to follow. To increase its effectiveness the *pinna* was often dipped into some nauseous mixture.

Hieronymus Mercurialis in his *De veneris* (1523) mentioned the use of a similar instrument in the treatment of poisoning, and Johann Arculanus in 1493 described and illustrated an instrument for forcing food down into the stomach. Thomas Willis (Fig. 8) in 1679 described a case in which he treated cardiospasm by feeding the patient and then passing down the esophagus a whale bone, at the end of which he had attached a sponge. He observed that "by this means he hath daily taken his sustenance for sixteen years and doth yet use the same Machine, and is yet alive, and well, who would otherwise perish for want of food." His description is a striking testimonial to the ingenuity of Willis and to the persistence of both physician and patient.

THOMAS WILLIS MEDIC. PROFESSOR. COLLEGII MED. LONDIN. ET SOCIET. REG. SOCIVS.

Fig. 8.—Thomas Willis.

Wilhelm Fabry, of Hilden, better known as Fabricius Hildanus (1560–1624), the "Father of German Surgery," described and illustrated a stomach sound which he employed for the extraction of small bones and other foreign bodies from the esophagus. Hieronymus Fabricius ab Aquapendente (1537–1619), the celebrated professor of anatomy and surgery at

Padua, fed patients through a stomach sound of silver and also employed this sound for nasal feeding. It is also stated that he employed this sound for cleansing the stomach (Fig. 9).

Around the end of the seventeenth or the beginning of the eighteenth century, an interesting instrument, the stomach brush, was devised for cleansing the stomach. The inspiration for this instrument was said to have come from "the wilds of America," where the savages treated disease by cleansing the stomach with a rope made of sharp leaves. This idea took hold in England, and in 1659 Rumsaeus published a book *Organum salutis, or An Instrument to Cleanse the Stomach,* the instrument consisting of a whale bone 2 to 3 feet in length, at the end of which was fastened a tuft of hair to wipe off the mucosa of the stomach. The treatment spread to the continent, where it soon achieved extraordinary popularity and was recommended for all stomach complaints. Laurenz Heister (1683–1758) gave an excellent illustration of a stomach brush in his *Institutiones chirurgicae* (Fig. 10). Heister, incidentally, made a more lasting contribution to diseases of the gastrointestinal tract. In 1711 he described the autopsy in the first case of unquestioned appendicitis with rupture of the appendix, an observation the great importance of which was not appreciated until after the work of Fitz in 1886.

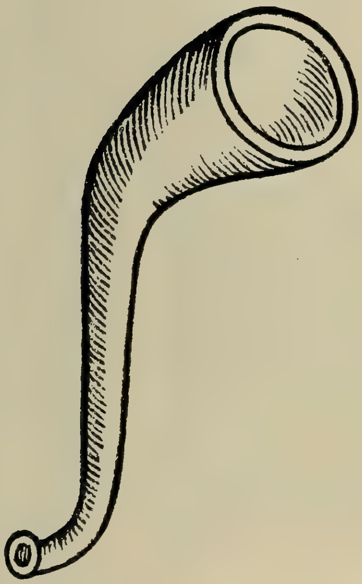

Fig. 9.—Gastric tube of Fabricius Hildanus.

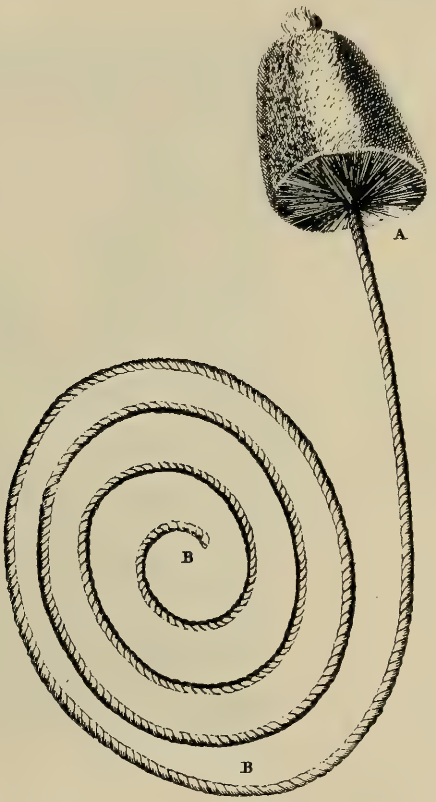

Fig. 10.—Stomach brush, from Heister's *Institutiones chirurgicae.*

Dominique-Jean Larrey, to whom Napoleon willed 100,000 francs with the notation, "To Larrey, the most virtuous man I have ever known," left in his surgical memoirs an interesting account of treatment with a stomach tube. The patient was a soldier who was wounded at the battle of Aboukir in 1808, by a bullet which passed through his throat and destroyed the epiglottis. He was unable to swallow and seemed doomed to starve, when Larrey passed "an elastic esophageal sound of gum" into his stomach and fed him through it. "This method, continued for a long time, saved the life of this soldier." This is one of the earliest accounts of feeding patients through a flexible stomach tube in contrast to feeding with metal tubes, described by Fabricius.

Fig. 11.—Adolf Kussmaul, from portrait by Lenbach.

The stomach tube was apparently first employed in cases of poisoning by Guillaume Dupuytren in 1810 and two years later by Philip Syng Physick. Both of these observers withdrew the stomach contents by attaching a syringe to the stomach tube after insertion. Their observations were followed by a deluge of articles describing "stomach pumps," the instruments of Jukes, Bush and Reed attracting the greatest attention.

The universal use of the stomach tube for gastric disease was doubtless due to the initiative of Adolf Kussmaul (Fig. 11). In 1867 Kussmaul saw a young peasant woman who had suffered from stomach trouble for fourteen years, was extremely emaciated and had a marked enlargement of the stomach with an ulcer of the pylorus. He treated his patient by pumping out the stomach and then irrigating it with Vichy water. The patient improved rapidly, gained more than 20 pounds and was completely cured.

In many cases dilatation of the stomach was cured by use of the stomach pump. The fame of the stomach pump soon spread far and wide in medical circles, and Kussmaul's advocacy of it led in some quarters to the erroneous assumption that he was its inventor. Kussmaul himself made no such claims but stated clearly that his stomach pump was designed by a Dr. Wyman in America and that he became acquainted with it by reading an article by Bowditch in the *American Journal of the Medical Sciences.*

Although the stomach sound, the stomach tube and the stomach pump were employed for centuries in the treatment of diseases of the stomach, the employment of the stomach tube for diagnostic purposes dates from the work of Wilhelm Leube in 1871. Korn remarked: "After Kussmaul in 1869 had introduced the stomach tube in therapeutics, it was the lasting achievement of Leube to have first employed the stomach tube for diagnostic purposes."

Leube gave his patients a breakfast consisting of soup, beefsteak and a bun and at the end of seven hours removed the stomach contents for examination. He studied particularly the duration of digestion and tested the strength of the gastric secretion. Leube's work was continued and amplified by van den Velden, who found no free hydrochloric acid in the presence of carcinoma of the stomach, and by Ewald and Boas, who determined the acidity of the gastric juice by titration with tenth normal sodium hydroxide. The latter observers introduced the Ewald-Boas test meal, which was widely employed by physicians for a generation.

No discovery in our generation has had such a profound influence on medical science as the discovery of the *x-ray* by William Conrad Roentgen in 1895. Its wide applicability was apparently not appreciated at first. Three months after Roentgen's announcement of his discovery, the *Journal of the American Medical Association* wrote that "the surgeons of Vienna and Berlin believe that the Roentgen photograph is destined to render inestimable services to surgery. . . . Half an hour is the shortest exposure possible, and most require one hour. The electric apparatus required is so expensive, $100.00 and upward, that few surgeons can use it yet in their private practice."

The first attempt to visualize the stomach was apparently made by John C. Hemmeter in the spring of 1896. Hemmeter introduced into the stomach a bag containing a solution of lead acetate and then made *x*-ray pictures of the stomach. Walter B. Cannon in December of the same year demonstrated the phenomenon of deglutition by feeding a goose capsules containing bismuth subnitrate. Cannon in 1897 was the first to employ free bismuth in an opaque meal in animals, the meal consisting of bismuth subnitrate mixed with bread, which was softened into a mushy mass with milk and water. Rumpel in the same year published the first account of the application of bismuth subnitrate to visualize the alimentary tract in man. Rumpel visualized a dilated esophagus by pouring into it a 5 per cent suspension of bismuth subnitrate. The same year Roux and Balthazard made the first studies on the human stomach, employing an opaque meal consisting of bismuth subnitrate suspended in water or syrup. Three months later Francis H. Williams, assisted by Cannon, administered bismuth subnitrate mixed with milk to a child aged ten years and made fluoroscopic studies of the stomach, outlining by tracing the various stages of gastric evacuation.

Five years later, in 1904, Rieder, of Munich, advocated the use of a meal similar to those employed by Roux and Balthazard and by Williams. After Rieder's work the opaque meal of gruel and bismuth became universally known as "Rieder's meal."

Further improvement in the *x*-ray apparatus, especially the advent of the transformer and the screen, gave great impetus to the roentgen study of the gastrointestinal tract. The study of the mucosal patterns was greatly facilitated by the employment of dilute solutions of bismuth and by the use of sticky emulsions of opaque substances. Bismuth subcarbonate was employed by Groebel and Meyer in 1908, instead of bismuth subnitrate, which occasionally contains poisonous impurities. In 1910 Bachem and Gunther introduced as an opaque medium barium sulfate, which is almost universally employed today.

With the perfection of *x*-ray technic it soon became possible to visualize gallstones under certain conditions. Carl Beck as early as 1899 exhibited a roentgenogram showing biliary and hepatic calculi. The most spectacular, as well as the most important, discovery in this field was the demonstration of Graham and Cole in 1924 that iodine salts of phenolphthalein were excreted in the gallbladder and cast a clear shadow. Their work marks an epoch in the development of our knowledge of hepatic diseases.

In 1869, eighteen years after Helmholtz had designed the first ophthalmoscope, Adolf Kussmaul attempted gastroscopy. Kussmaul persuaded a sword swallower to swallow a straight metal tube 47 cm. long and 13 mm. in diameter, into which he then inserted a light. The attempt was not successful, because, as Kussmaul wrote, the source of light was too far removed from the tip of the tube and fluid collected at the tip and obscured his vision. Ten years later Max Nitze, who had two years previously constructed a successful cystoscope, designed a gastroscope with the source of light at its tip and obtained clear views of the gastric mucosa. Johann von Mikulicz-Radecke, an eminent surgeon, constructed, in 1881, a gastroscope which was such an improvement over previous instruments that he is commonly referred to as "the founder of gastroscopy."

The instrument of Mikulicz was followed by numerous others, almost every one being an improvement over its predecessor. Among the best known of these instruments were those of Rosenheim, Kelling, Kuttner, Jackson and Laening and Stieda. The recent introduction of a flexible gastroscope by Wolf and Schindler has given a great impetus to gastroscopy, hitherto somewhat neglected. Eusterman in 1938 went so far as to state that "accumulating experience also attests the indispensability of competent gastroscopic examination in daily gastro-enterologic practice."

This brief survey of the history of our knowledge of digestive diseases shows its intimate relation to all fields of medicine. Periods of stagnation in medicine are reflected in the lack of progress in the knowledge of diseases of digestion; eras of great advance are likewise reflected. Eras of vain speculation have retarded progress; confused thinking in general medicine corresponds to confused views on digestive diseases. Conversely, gastroenterology has, like general medicine, profited by all the great discoveries in anatomy, physiology, chemistry and physics. As general medicine advances further, so will gastroenterology advance; when general medicine halts, it also will mark time.

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CHAPTER II

THE ANATOMY OF THE GASTROINTESTINAL TRACT

As a medical discipline anatomy may be viewed historically as comprising three periods: (1) that before Lister, when virtually all anatomic knowledge was acquired from the dead human or other mammalian body; (2) that after Lister and before Roentgen, when the surgeon-anatomist had constantly to revise his knowledge by observation of the living body at operation; (3) that after Roentgen, whose contribution of ultravision has revealed the living body as kaleidoscopic in diversity, especially with reference to development, growth, nutrition, tonus, posture and other physiologic states and with reference to constitutional and racial types.

This being the case, it no longer suffices to learn meticulous but withal static descriptions of the human mechanism. Anatomy of the cadaver is useful—even indispensable—and will always be so, as the point from which to make one's departure. Yet with every portion of the body, and to a large extent with the viscera, the point of departure and the experiences of the surgeon, clinician and roentgenologist have greatly enriched the field of knowledge of the anatomist. In turn the researches in anatomy, physiology and allied subjects, *e. g.*, on the glands of internal secretion, the reproductive cycle, nutrition, the role of the pancreas in diabetes and of the liver in anemia, have much expanded the scope of medical practice.

DESCRIPTIVE AND TOPOGRAPHIC ANATOMY

For purposes of description it is necessary to formalize the digestive tract with usual terminology and topographic definitions, even though these may apply only incidentally to the more mobile parts of the tract. The following "cadaver anatomy" and commentaries may readily be distinguished as the aforesaid points and departures therefrom.

The extra-abdominal parts of the digestive tract are the mouth, pharynx and esophagus. The mouth, where food is sampled by taste, ground by the teeth and prepared for swallowing by the tongue and cheeks, is the field of study of oral surgery and dentistry, and its study cannot be undertaken here. So, too, the pharynx, with its complex muscular walls, respiratory and digestive communications and lymphoid aggregates, is the special problem of the otolaryngologist. Only the esophagus will be discussed here, and briefly.

The esophagus extends from the pharynx (opposite the sixth cervical vertebra) to the cardiac orifice of the stomach (opposite the tenth or eleventh thoracic vertebra). Its total length includes three topographic divisions, the cervical, thoracic and abdominal, and is 10 to 12 inches (25 to 30 cm.). Of clinical significance are the following measurements, taken from the upper incisor teeth: to the esophagus, 6 inches (15 cm.); to the level of crossing of the esophagus by the left bronchus, 9 inches (22.5 cm.); to the esophageal opening in the diaphragm, 14 to 15 inches (35 to 37.5 cm.); to the cardiac orifice, or opening of the esophagus into the stomach, 16 inches (40 cm.). These measurements are of special interest in gastroscopy.

Excepting the pylorus, the esophagus is the narrowest part of the digestive tract and normally shows three special constrictions: (1) at its beginning, (2) at the point where it is crossed by the left bronchus, (3) at its passage through the diaphragm. The trachea to its bifurcation (fifth thoracic vertebra) lies in front of the esophagus; in the interval between the trachea and esophagus the recurrent laryngeal nerve on either side passes up to the larynx. The thoracic aorta is at first to the left of the esophagus; at the eighth thoracic vertebra it begins to turn behind it, and where the two pass through the diaphragm the aorta is not only behind but fractionally to the right. The thoracic duct passes through the aortic hiatus in the diaphragm and in the upper parts of its course lies behind the esophagus. Through the esophageal hiatus in the diaphragm pass the vagus nerves, the left in front of and the right behind the esophagus. These nerves of the vagus are retained on the walls of the stomach, thus clearly indicating the direction of rotation of that organ (*vide infra*).*

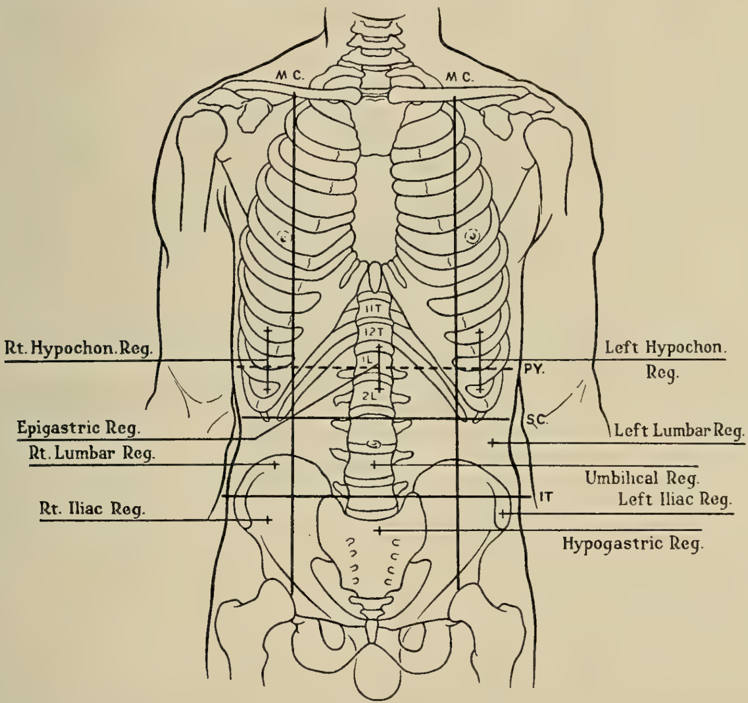

FIG. 12.—Frontal body outline and projection of skeleton, showing planes and topographic regions of abdomen. *SC* designates subcostal plane, horizontal, below most dependent portion of costal margin (tip of tenth rib); *IT*, intertubercular plane, horizontal, through tubercles of iliac crest; *PY*, transpyloric plane (Addison), horizontal, about midway between umbilicus and xiphisternal junction; *M.C.*, midclavicular plane, perpendicular, through midpoint of clavicle.

Abdominal parts of the digestive tract are customarily described in topographic relation to named regions of the abdomen (Fig. 12). A modern way to demarcate lateral from medial regions is to use the curved line formed by the lateral border of the rectus abdominis muscle on either side; but in persons even slightly corpulent the border of the rectus is not readily defined.

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* It has been shown that the esophageal plexus has a most constant structural basis and that each vagus nerve supplies fibers to both anterior and posterior surfaces of the stomach (McCrea, E. D.: *J. Anat.* **59**, 18, 1924).

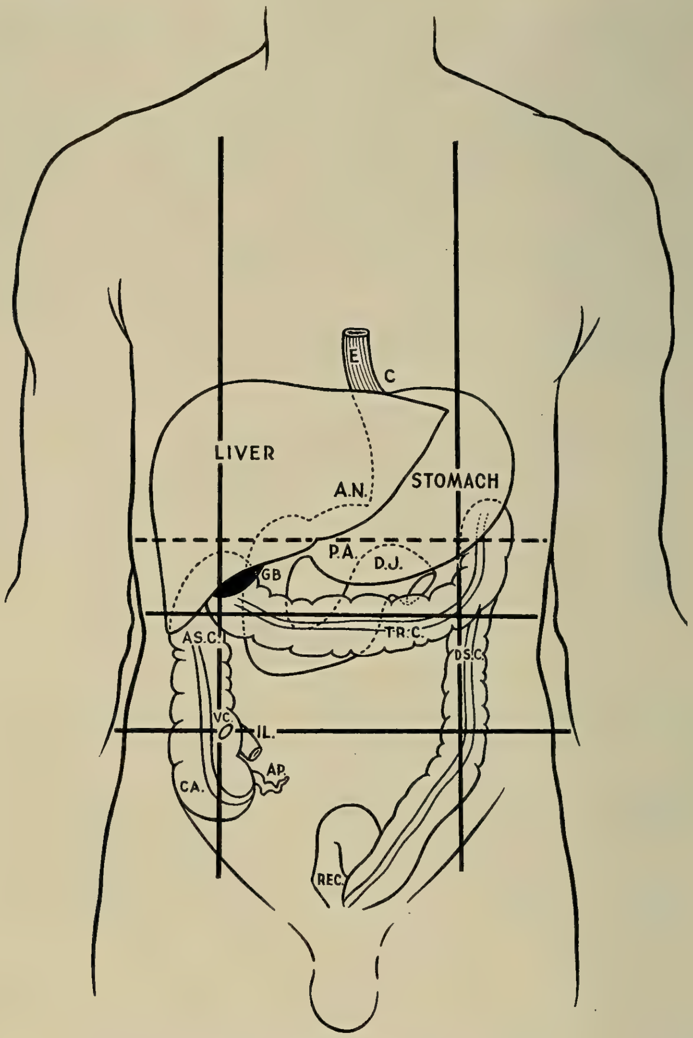

Fig. 13.—Frontal body outline and planes as in figure 12, showing the larger abdominal viscera in relation to each other and to the planes. *E* designates esophagus; *C*, cardia of stomach; *A.N.*, angular notch, or gastric angle; *P.A.*, pyloric antrum; *GB*, gallbladder; *D.J.*, duodenojejunal flexure; *IL.*, terminal portion of ileum; *VC.*, ileocecal valve; *As.C.*, ascending colon; *Tr.C.*, transverse colon; *Vs.C.*, descending colon; *Rec.*, rectum.

Stomach (Gaster, Ventriculus).—The stomach is subject to great variation in shape, size and position, depending on its state of filling, tonus and peristaltic activity, as well as on bodily posture and habitus. Usually distinguishable are the following named parts: *A*, the first two-thirds (*pars cardiaca*), comprising the *body* (1) with an upper left expansion, the *fundus* (2), the latter forming an angle with the esophagus and the *cardia* (3); *B*, the last third (*pars pylorica*), variously bent to the right, upward and backward from the body (1). This often presents a dilatation, the *pyloric* *antrum* (4) and leads directly to the *pyloric canal* (5). This in turn communicates with the duodenum, the transition being marked by a heavy circle of muscle, the *pyloric sphincter* (6). Separating the anterior from the posterior surface of the stomach are: below and to the left the *greater curvature* (7), from which depends the *greater omentum;* upward and to the right the *lesser curvature* (8), to which attaches part of the *lesser omentum*

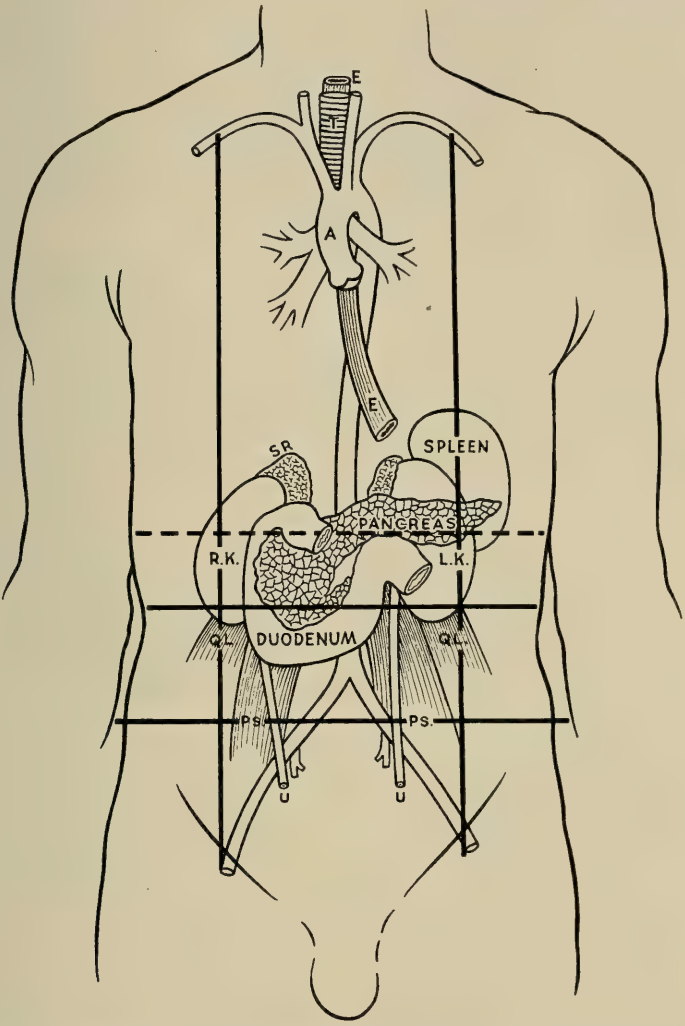

FIG. 14.—Frontal body outline and planes as in figure 12, showing deeper abdominal viscera in relation to each other and to planes. *E* designates esophagus; *T*, trachea; *A*, aorta; *R.K.*, right kidney; *L.K.*, left kidney; *U*, ureter; *SR*, suprarenal gland; *Q.L.*, quadratus lumborum muscle; *PS.*, psoas major muscle.

(*hepatogastric ligament*) and which shows something of an indentation, the *angular notch* (*gastric angle*) (9), which demarcates the cardiac from the pyloric part of the stomach. A corresponding notch on the greater curvature may be indicated.

Another descriptive terminology, introduced by Forssell (1913), is securely founded on a large series of x-ray studies of the living stomach (Fig. 15, *A*). The protean nature of the stomach contour is strikingly portrayed by Forssell in his silhouets of induced opacities, representing various states of filling of the stomach (Fig. 15, *B*).

The form of the stomach shown in figure 13 is one often used for descriptive purposes, but is rarely that found in x-ray pictures of the living body. When empty, or nearly so, the stomach is a narrow tube, constantly somewhat distended at the fundus by residual gas. In the erect body the stomach is frequently J shaped ("fish-hook" stomach), the long limb of the J being the cardiac part and the short limb the pyloric part. In the recumbent body the fundus is more distended and displaced to left, and the direction of the cardiac part is distinctly oblique, the contour approaching that of the "cow-horn" stomach. However, it is seldom true that in the same person the characteristic fish-hook and cow-horn shapes are merely transient contours induced by change of posture.

Because of great variation in the shape and size of the stomach it is not possible to give precise definition to its position. The most nearly fixed points are its extremities, *i. e.*, the cardia and pylorus. The latter, however, is by no means immovable. In the recumbent body it lies to the right of the first lumbar vertebra, in or near the "transpyloric plane" (of Addison); this plane (Fig. 12) is about midway between the xiphisternal junction and umbilicus. In the erect body the pylorus may lie opposite the second or third lumbar vertebra or much lower.

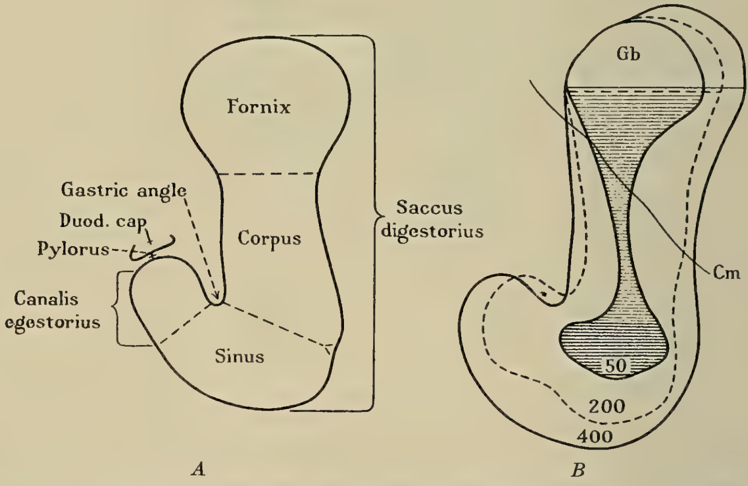

FIG. 15.—Contours of stomach and descriptive terminology according to Forssell (1913). *A*, the *canalis egestorius* corresponds approximately to the pyloric canal and the *saccus digestorius* to the rest of stomach. *B* shows the outlines of the stomach in the erect body, shown by x-ray after ingestion of 50, 200 and 400 cubic centimeters of a bismuth suspension. *Cm* designates the costal margin.

The stomach occupies large portions of the epigastric and left hypochondriac regions (Fig. 13) but when distended, especially in the erect body, it may descend to the umbilical region or into the pelvis (hypogastric region). The fundus is separated from the heart and left lung by the left dome of the diaphragm and with the latter moves in respiratory excursions for 2 to 6 centimeters. The shape and position of the stomach have been found by Mills (1917) to be correlated with bodily habitus (Fig. 16).

In the erect body the support of the stomach is mainly by the transverse

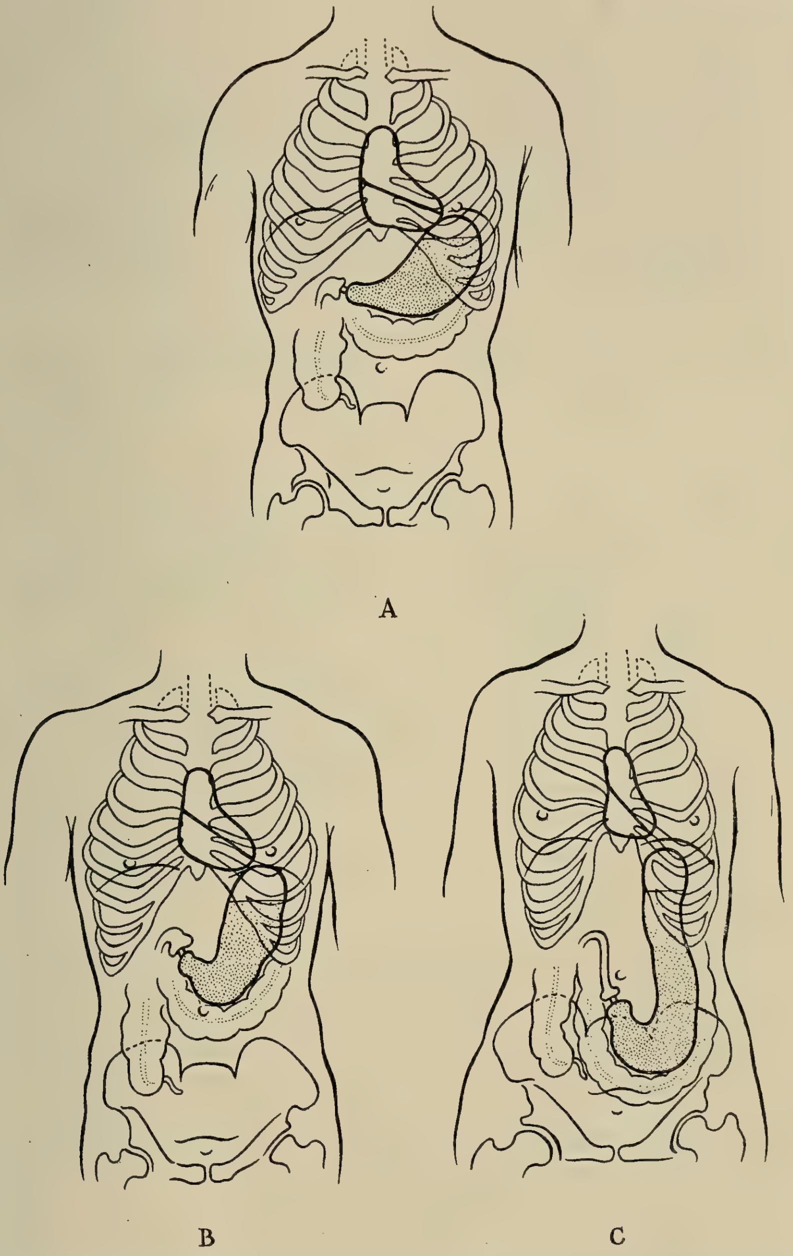

Fig. 16.—The shape and position of the stomach correlated with bodily habitus (adapted from Mills, 1917). In heavily built persons with the upper part of the abdomen and thorax broad (hypersthenic type, *A*), the stomach is high and oblique. In slender persons with the upper part of the abdomen and thorax narrow (asthenic type, *C*), the stomach is low and linear. Intermediate types (*B*) are found to show intermediate positions and directions of the stomach.

colon and mesocolon, these in turn being upheld by the small intestine acting as hydrostatic pressure against the abdominal wall. In the recumbent body the stomach rests on the so-called stomach bed, *i. e.*, the following structures, from left to right: spleen, left crus of diaphragm, below this the left kidney and suprarenal gland, below these and extending farther to right the pancreas and below the pancreas over a large area the transverse mesocolon. The posterior surface of the stomach in contact with the stomach bed is covered by the peritoneum of the omental bursa (lesser sac).

The small intestine, comprising the retroperitoneal duodenum and the mesenteric jejunoileum, extends from the pylorus to the ileocecal junction. This length of digestive tube measures about 23 feet (7 meters) when removed at autopsy but when fixed in solution of formaldehyde without removal it is a little over 13 feet (4 meters). Normal limits of length of the living small intestine have been variously estimated, but are not precisely known.

Duodenum.—The duodenum (etymology: 12 fingerbreadths long) is about 8 to 10 inches (20 to 25 cm.) in length and is the widest part of the small intestine (4+ cm. in diameter). Its usual C shape suggests three topographic divisions: (1) the upper part of the C (*pars superior*), 5 centimeters long, leads to the right and backward from the pylorus to the first bend (*superior flexure*); (2) the middle part of the C (*pars descendens*), 7 to 8 centimeters, receives the pancreatic and common bile ducts and leads to the second bend (*inferior flexure*); (3) the lower part of the C (*pars inferior*), 12 to 13 centimeters, is subdivided into a *horizontal* part (10 cm.) and an *ascending* part (2 to 3 cm.), which latter ends in the duodenojejunal flexure.

Though usually thought of as relatively fixed, the duodenum may appear on the *x*-ray film as various unaccountable loops and bends. Also it is not invariably C shaped. The inferior part may pass directly from the inferior flexure to the beginning of the jejunum, forming a V. Or it may make a short horizontal connection with the jejunum, forming an L. The pylorus and duodenojejunal flexure may be so close together as to form an O; or they may be so far apart as to form a prone U. However, since three parts of the duodenum are usually distinguishable, further description will be based on the C shape.

The duodenum occupies the right half of the epigastric region (Figs. 13 and 14), only its horizontal part reaching the umbilical region and only its ascending (terminal) part crossing the midline. The superior part is fairly mobile, its position depending largely on the state of filling of the stomach; with the stomach empty, it lies horizontally to the right of the first lumbar vertebra or disk; with the stomach variously filled and the pylorus pushed downward and to the right, it lies obliquely and at lower levels. The pylorus usually appears as a slight protrusion into the duodenum with resulting distention of the latter to form the *duodenal antrum* or *"cap,"* a conspicuous feature in *x*-ray silhouets of this region.

The *superior* part of the duodenum is directly below the neck of the gallbladder and quadrate lobe of the liver; *anterior* to it are the liver and the transverse colon, *inferior* to it are the pancreas and common bile duct, hepatic artery and portal vein. These last three structures pass *behind* the duodenum and by way of the lesser omentum (hepatoduodenal ligament) reach the porta hepatis, in this transit forming the peritoneum-covered *anterior* boundary of the epiploic foramen (of Winslow). Other peritoneum-covered boundaries of this foramen are: *inferior*, the duodenum (pars superior); *posterior*, the inferior vena cava; *superior*, the caudate process of the caudate lobe of the liver.

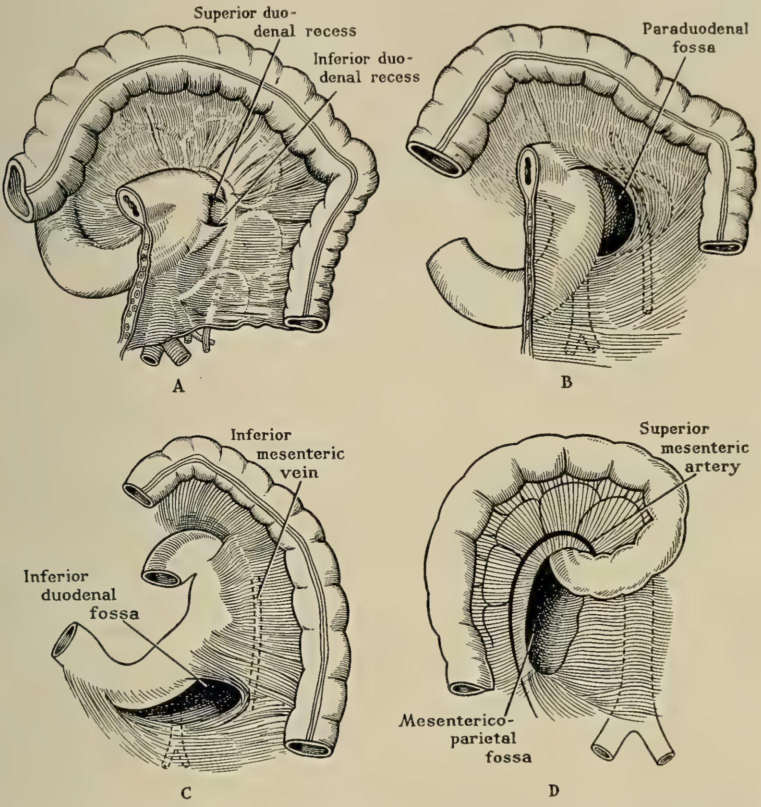

FIG. 17.—Drawings showing: *A*, The *superior duodenal recess*, opposite the second lumbar vertebrae (incidence, 50 per cent), usually about 1 inch (2.5 cm.) deep, which opens downward and is formed by a triangular fold of peritoneum extending from the duodenum leftward to the posterior abdominal wall; and the *inferior duodenal recess*, opposite third lumbar vertebra (incidence reported by different authors, 20 to 75 per cent), which opens upward, and usually is larger than the superior recess but is formed by a similar fold of peritoneum. *B*, *Paraduodenal fossa* (of Landzert) (incidence, 20 per cent), not often found in adults never with other fossae of the duodenum. This opens to the right and upward; its covering fold of peritoneum contains the inferior mesenteric vein. *C*. *Inferior*, or *retroduodenal*, *fossa*, often a shallow depression beneath the transverse part of the duodenum, but may extend as a deep pouch directed upward under the duodenum. *D*, *Mesentericoparietal fossa* (of Waldeyer), rare, usually in the first part of the jejunal mesentery just below the duodenum. This is larger than the other culs-de-sac in the region of the duodenum, and differs by opening to the left, its blind end directed to the right and downward. Its covering fold contains the superior mesenteric artery or a branch, the ileocolic artery; peritoneum of the left side of the mesentery lines the fossa.

The *descending* part of the duodenum in its passage along the right side of the first to third lumbar vertebrae has only an anterolateral covering of peritoneum, and this is to some extent interrupted by the transverse colon. *Posteriorly* this part of the duodenum rests against the right renal vessels, kidney, ureter and psoas muscle; *superiorly*, above the colon, it may lie against the gallbladder; *inferiorly,* below the colon, it may be in contact with coils of small intestine; *medially* it is bound to the head of the pancreas, through which passes the common bile duct to open with the pancreatic duct (of Wirsung) into the duodenum about 4 inches (10 cm.) from the pylorus. At a variable distance (0.9 to 3.5 cm.) above the opening of these two ducts the accessory pancreatic duct (of Santorini) enters the duodenum. Along this concave border of the duodenum is the loop between the superior and inferior pancreaticoduodenal arteries.

The *horizontal* part of the duodenum, lying on the third lumbar vertebra, is invested with peritoneum except where it (and the uncinate process of the pancreas) are crossed by superior mesenteric vessels and the root of the intestinal mesentery. After surgical manipulation in the abdomen the superior mesenteric vein may become so engorged as to constrict the duodenum at the aforementioned point of crossing; to this constriction is attributed the acute gastric dilatation sometimes resulting from abdominal operations. The *ascending* (terminal) part of the duodenum, lying on the left renal vessels, aorta and psoas muscle, has at its right side the superior mesenteric vessels and uncinate process of the pancreas; to the left and anteriorly it is covered by peritoneum. The *duodenojejunal flexure,* usually at the level of the second lumbar vertebra, lies below and against the root of the transverse mesocolon and body of the pancreas.

The terminal part of the duodenum is firmly upheld by the suspensory muscle of the duodenum (ligament of Treitz), a narrow band of smooth muscle extending from the right margin of the aortic hiatus and the left crus of the diaphragm to pass in front of the celiac plexus, to the left of the celiac artery and behind the pancreas to reach the duodenojejunal flexure. Here it is said to mingle with the muscles of the intestinal wall and to send some fibers beyond the intestine into the mesentery.

Peritoneal reflections on the left side of the ascending part of the duodenum present various folds and fossae (Fig. 17). These fossae are of surgical interest, since they may provide sites for internal hernia and strangulation. However, it should be recalled that loops of intestine in these fossae, like those entering the omental bursa *via* the epiploic foramen, may not always be hernias in the usual sense but are sometimes inclusions resulting from errors of rotation.

Jejunoileum.—The jejunoileum is the very mobile, mesenteric part of the small intestine, extending from the duodenojejunal flexure to the ileocecal junction. It is customary to regard the jejunum as the upper two-fifths of the mesenteric intestine and the ileum as the lower three-fifths, but there is, in fact, no external demarcation between the two parts; rather, the transition is in the nature of a gradient. Characteristic samples of jejunum and ileum differ in that the jejunum has thicker walls and is wider and more vascular; also the mucosa (discussed later) has certain features peculiar to one or the other part. The fact that the ileum, especially in its lower portion, is distinctly more narrow than preceding levels of the intestine favors impaction of gallstones and ingestion of foreign bodies in this region.

The practical problem of the surgeon, confronted with loops of small intestine, is to ascertain whether he is dealing with upper, middle or lower parts. This is difficult because of the considerable variation in length of the intestine and the wide range of movement due to peristaltic activity.

It may be said as a rule that the upper third of the mesenteric intestine occupies the left hypochondriac region, the middle third the umbilical region and the lower third the right iliac and hypogastric regions.

Of more diagnostic value in distinguishing parts of intestine is the free (intestinal) border of the mesentery. In the upper third (jejunal region) mesenteric fat does not extend up to the intestinal attachment of the mesentery; in the resulting interval of peritoneum the bloodvessels are plainly visible. In the lower third (ileal region) fat reaches to or onto the intestine, giving the mesentery a distinctly thick appearance (Monks, 1913).

A further diagnostic point is the disposition of arteries in the mesentery. The superior mesenteric artery supplies twelve to twenty intestinal branches, which course between peritoneal layers of the mesentery to reach the jejunoileum. As vessels approach the intestine they bifurcate, and branches of contiguous arteries unite to form primary arches, the convexity of which is directed toward the intestine. In the upper fourth (proximal part of the jejunum) the arches are entirely *primary* and their branches to the intestine are *long*. At subsequent levels primary arches give rise to secondary, then secondary to tertiary, etc., until in the mesentery of the lower ileum there may be as many as *five* tiers of arches, whose branches to the intestine are very *short*. Thus there is an increasing gradient of complexity in arterial patterns from beginning to end of the jejunoileum. On the other hand, there is a decreasing gradient in size and length of branches from the arches, the larger and longer supplying the upper parts (jejunum) and the smaller and shorter the lower parts (ileum).

Studying collateral circulation in the mesentery of the rat, Weyrauch and De Garis (1937) showed by interrupting vascular patterns seriatim that about three-fourths of the direct blood supply to the intestine could be removed without producing infarction. Thus in the rat there is a wide margin of safety in the blood supply to the intestine, owing to free anastomosis by way of the arterial arches. Since the arches in man are far more elaborate than in the rat, an even wider margin of safety might be anticipated. However, when a segment of intestine has its blood supply isolated by pressure, as in the presence of strangulated hernia, volvulus or intussusception, the mechanical factors are wholly different, since then no collateral circulation is available.

Opposite the original termination of the superior mesenteric artery and on the antimesenteric border of the ileum is sometimes found an outpouching of the intestine, the *diverticulum ilei* (of Meckel), persisting part of the vitellointestinal duct. Meckel's diverticulum occurs much more frequently in males than in females; its length varies from 1 to 13 centimeters, and it has been found 15 to 360 centimeters from the ileocecal junction. It usually ends free and unattached, though it may have a small mesentery; at times it is adherent to adjoining coils of intestine, or it may lead by an attenuated band to the umbilicus. Attached and attenuated forms of the diverticulum have been known to cause intestinal strangulation, and intussusception may start from diverticular invagination. The walls of the diverticulum being much thinner than those of ileum, inflammation results more readily in perforation in the former. Symptoms of such inflammation are similar to those of appendicitis, but the hazards of general peritonitis from perforation are much greater, since the diverticulum usually lies in the midperitoneal cavity, where the safeguards adhesion and localization are less likely to occur.

The root of the mesentery, about 6 inches (15 cm.) long, passes obliquely to the right from the duodenojejunal flexure across the transverse part of the duodenum, the great vessels, vertebral column and right ureter to reach the ileocecal junction in the right iliac region. At times there is fusion of the mesentery with the parietal peritoneum in such a way as to immobilize the terminal few inches of the ileum. Or in this same region there may be a thickened band of peritoneum (Lane's ileal membrane) extending from the right iliac fossa to the antimesenteric border of the ileum. Slight kinking due to Lane's membrane is said to predispose to obstruction at this point, but there is no general concurrence in this view.

Large Intestine.—The large intestine forms the right, upper and left sides of a rectangular frame, with the mesentery of the jejunoileum as a diagonal. The right side of the frame is the *ascending colon*, the upper side the *transverse colon* and the left side the *descending colon;* the *sigmoid* (*pelvic*) *colon* may be viewed as the lower side of the frame bent out of alinement. This "intestinal frame" is the larger of two great divisions of the abdominal cavity; the other division, lying directly above it and separated from it by the transverse colon and mesocolon, is the gastrohepatic "spherical segment." Thus, for topographic orientation the most important features of the abdominal cavity are the transverse colon and its mesocolon, since these are the horizontal plane demarcating the lower, intestinal zone from the upper, gastrohepatic zone.

This being so, it is highly important to find something other than size by which the colon may be distinguished from the jejunoileum. Three external characters of the colon are available: (1) *taeniae coli*, three bands of longitudinal muscle, each nearly ½ inch (12 mm.) wide, almost equidistant one from the other along the surface of colon; (2) *haustra*, or sacculations, of the walls of the colon, produced by a given length of wall being adapted to a lesser length of taeniae; (3) *appendices epiploicae*, small fat-filled appendages of peritoneum, studding the exposed surface of colon and most numerous along the taeniae.

Cecum.—The cecum is the cul-de-sac of the large intestine at and below the ileocecal junction. Varying in size and shape (Fig. 18), it is usually about 3 inches (7.5 cm.) wide and 2½ inches (6 cm.) long, is enclosed by peritoneum (in 10 per cent of cases adherent posteriorly) and lies on the iliacus muscle in the right iliac fossa. In the erect body it lies at the brim of or within the pelvis. The *ileocecal valve* (*valvula coli*) appears as the ileum, directed obliquely upward and to the right, protruding into the posteromedial wall of the cecum. The opening, about ½ inch (1.2 cm.) long, is usually a horizontal slit between prominent upper and lower lips; its topographic position is fractionally to the right of and below the midpoint of the spinoumbilical line. The ileal protrusion is often said to act as a valve in preventing the cecal contents from returning to the ileum; however, *x*-ray demonstrations prove beyond question that the so-called valve has no such function. The most usual form of intussusception is that in which the ileocecal valve and ileum telescope into the cecum, the valve always at the advancing end of the involution.

Vermiform Appendix.—The vermiform appendix (*processus vermiformis*) is a blind tube, narrow, coiled and variable in length; usually about 3½ inches (8.8 cm.) long, it varies from ¾ to 9 inches (1.8 to 22.5 cm.). It represents the original apex of the cecum and is therefore the focal point of the taeniae; the most available of the taeniae, the anterior or taenia libera, should be followed as the best guide to the root of the appendix. Considering the cecum and appendix as at one time in symmetric relation (Fig. 18), there has occurred such a differential growth distention of the right ventrical part of the cecum that the apical appendix has acquired a left dorsal position. Its connection with the cecum is fairly constant at 1 to 1½ inches (2.5 to 3.7 cm.) below the ileocecal junction; infrequently it lies much closer to, or even behind, this junction. Pain attending inflammation of the appendix becomes acutely localized at McBurney's point.*

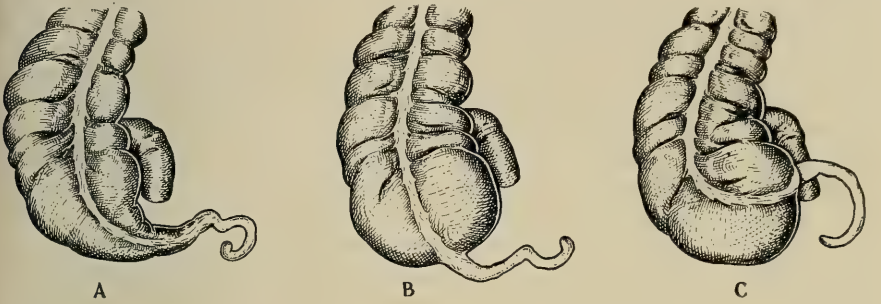

Fig. 18.—Series of the cecum-appendix without peritoneal investment: *A*, Cecum-appendix in the newborn, the apex of the conical cecum giving rise to the appendix. The adult cecum, when empty and contracted, may approach this type. *B*, Cecum-appendix during early years of childhood; the cecum is bilaterally sacculated. *C*, The usual type of the adult cecum-appendix; as a result of growth distention of the right ventral wall of cecum the appendix arises dorsally and to left. (After De Garis, arranged from *Annals of Surgery*.)

The direction of the appendix was reported in 10,000 cases (Wakeley) as retrocolic or postcecal in 65 per cent, pelvic in 31 per cent and rarely postileal, preileal or subcecal. According to my experience (1941) and that of many others (Kelly and Hurdon, 1905), the appendix takes the following directions, in order of frequency: (1) to or into pelvis (4 to 5 o'clock); (2) toward spleen (2 to 3 o'clock); (3) behind cecum (9 to 12 o'clock); (4) under cecum (7 to 8 o'clock). More important, however, are two general categories of appendix, the congenitally adherent and the freely mobile, this latter having no constant direction. The appendix is attached to the left layer of ileal mesentery by a sickle-shaped mesoappendix, within the free border of which pass the appendicular twigs of the ileocolic bloodvessels. The mesoappendix and appendicular bloodvessels, being directly over-lain by the terminal part of the ileum, may be subject to ileal pressure, regarded as a factor in gangrene of the appendix.

Peritoneal folds and fossae of the ileocecal region are important by reason of the surgical accidents peculiar to this region. The *ileocolic fossa*, also called the superior ileocecal fossa (incidence 33 per cent), opens to the left and downward and is formed by a small fold of peritoneum arching over the ileocecal junction from the ileal mesentery to the colon and cecum. The edge of this fold encloses the anterior cecal branch of the ileocolic artery, which branch occasionally supplies the appendix. The (inferior) *ileocecal fossa* (incidence 85 per cent) also opens to the left and downward and is formed by a crescentic fold from the terminal part of the ileum to the cecum and mesoappendix; this fold, known as the "bloodless fold of Treves," contains no visible bloodvessels. The *retrocecal* (retrocolic or subcecal) *fossa* (incidence 10 per cent) is a peritoneal pouch beneath the cecum, at times extending far upward beneath the ascending colon. A retroappendix sometimes lies in this fossa but more frequently exists unattended by peritoneal folds and fossae.

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* In current literature are at least three definitions of McBurney's point. McBurney's own specifications follow (*New York M. J.* **50**, 683, 1889): ". . . the ascertaining, by the pressure of a single finger-tip, that the point of greatest tenderness is, in the average adult, almost exactly two inches from the anterior iliac spine, on a line drawn from this process through the umbilicus." According to McBurney, this point lies over the root of the appendix. However, *x*-ray tracings have shown that McBurney's point and the root of the appendix do not usually coincide; in topography of the living subject the root of the appendix appears highly variable, though usually within the right iliac region (Barclay; De Garis, 1941).

Ascending Colon.—The ascending colon passes from the cecum to the under-surface of the liver at an angle between the quadratus lumborum and psoas muscles; just lateral to the gallbladder it bends sharply to the left and downward, forming the *hepatic flexure.* It is about 8 inches (20 cm.) long and occupies the right lumbar and hypochondriac regions. Usually covered by peritoneum on the front and sides only, in some cases (26 per cent, according to Treves) it has a short mesentery. As a rule confined to such cases is a vertical peritoneal fold (Jackson's pericolic membrane) passing from the posterior part of the right abdominal wall to the anterior taenia of the ascending colon and cecum. This fold, often thin and translucent, lodges bloodvessels that are long, slender and parallel. Other inconstant peritoneal folds pass from the ascending colon to adjacent parts, *e. g.*, the hepatocolic, cystocolic and phrenicocolic areas and the sustentaculum hepatis; this last extends horizontally from the right side of the colon to the abdominal wall just above the iliac crest and forms an apparent shelf for the right margin of the liver.

Transverse Colon.—The transverse colon, 16 to 20 inches (40 to 50 cm.) long, forms an arch convex forward and downward between the hepatic and splenic flexures, thus crossing the umbilical region from the right to the left hypochondrium. In the recumbent body the colic arch is approximately tangent to a plane horizontal through the highest part of the iliac crests, but in the erect body the arch may lie anywhere between the subcostal plane and the pelvis. It is constantly seen by *x*-ray that wherever the most dependent part of the stomach lies, the transverse colon will be found below it, often immediately so (Fig. 16). There are, however, occasional V-shaped and U-shaped bends of the transverse colon, apparently intrinsic, possibly congenital and always directed downward, even as far as the pubes or into the pelvis, but not invariably related to the stomach contour.

The transverse colon is in large part surrounded by peritoneum and supported by the mesocolon—only where it crosses the descending part of the duodenum and head of the pancreas does it lack posterior peritoneum. The transverse colon and mesocolon have been noted as forming part of the "stomach bed" (*vide supra*); above them are the liver and gallbladder to the right and the spleen to the left. Where the mesocolon approaches the posterior abdominal wall its two layers split along the anterior border of the pancreas, the upper layer being continuous with the peritoneum of the lesser sac and the lower layer with that of the greater. Lying on and depending from the transverse colon is the greater omentum, often heavily leafed with fat.

The *splenic*, or *left, flexure* is one of the few relatively fixed points in the abdominal part of the digestive tract, in this respect comparable to the cardia of the stomach and the duodenojejunal flexure. It is held in place by the *phrenicocolic ligament*, a peritoneal fold from the colon to the diaphragm at the level of the tenth or eleventh rib. Since it supports the spleen, it is called the *sustentaculum lienis.* The transverse colon rises abruptly and passes deep into the left hypochondrium to reach the height of the splenic flexure, and the flexure itself is usually very acute. In comparison, the *hepatic,* or *right, flexure* is at a lower and more variable level, depending on the state of filling of the ascending or the transverse colon or both. Thus, in the recumbent body the hepatic flexure lies under the ninth costal cartilage (level of the second lumbar vertebra); in the erect it reaches the subcostal plane or lower levels.

Descending Colon.—The descending colon, 10 to 12 inches (25 to 30 cm.) long, extends from the splenic flexure to the sigmoid colon at the brim of the pelvis, lying successively in the left hypochondriac, left lumbar and left iliac regions. Like the ascending colon, it is usually covered only on the front and sides by peritoneum but is mesenteric, especially in its iliac portion, in 36 per cent of cases (Treves). The segment from the iliac crest to the pelvic brim has been designated as the *iliac colon* (Jonnesco).

Sigmoid (Pelvic) Colon.—The sigmoid (pelvic) colon, the last mesenteric part of the large intestine, is about 16 inches (40 cm.) long and extends from the descending colon to the rectum in an alleged sigma loop. Actually it begins at the pelvic rim over the psoas major muscle, descends on the left pelvic wall to the pelvic floor, crosses to the right pelvic wall, then bends on itself, recrosses to the midline and joins the rectum opposite the second or third sacral vertebra. It is completely pelvic in 90 per cent of adults; in 10 per cent it bends upward to or toward the umbilicus, a position usual in infants.* Since the beginning and end of the sigmoid loop are often close together and the mesentery may be unduly long, axial rotation and volvulus occur more frequently here than elsewhere in the intestine. The root of the mesentery may lodge the *intersigmoid recess*, a pouch of variable size opening to the left and downward, rarely the site of hernia and strangulation. The angular junction of the sigmoid and rectum, the narrowest part of the whole colon, may be the site of stricture. For this and other surgical conditions of the pelvic bowel the upper part of the sigmoid is often brought into the abdominal wall in the left iliac region and opened to form an artificial anus (colostomy).

Rectum.—The terminal part of the intestine, the rectum, is so called because in certain mammals like the pig, dissected by early anatomists, it is straight. In man the rectum follows the sacrococcygeal curve, with the concavity forward, and then bends backward to form the *anal canal;* also, most marked when the rectum is distended, are three lateral curves, with the concavity (1) to the left, (2) to the right and (3) to the left. The upper part of rectum is 4 to 4⅘ inches (10 to 12 cm.) long; that of the lower part, or anal canal, 1 to 1⅖ inches (2.5 to 3.5 cm.). The anterior relations are: in the male, to the trigone of the bladder, seminal vesicles, ducti deferentes and prostate; in the female, to the vagina and cervix uteri. The first third of the rectum is covered by peritoneum on the front and sides; the second part on the front only. The peritoneal reflection in the male, from the rectum to the bladder, forms the *rectovesical pouch;* the same reflection in the female, to the vagina and uterus, forms the *rectouterine pouch* (of Douglas). The last third of the rectum is below the peritoneum; after bending to form the anal canal it passes downward and backward through the pelvic diaphragm (levator ani muscle) to terminate in the anus, the caudal aperture of the digestive tract.

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* These figures must be regarded as taken from cadaver census. In x-ray silhouets the living adult sigmoid appears above the pelvic brim in many more than 10 per cent of cases.

Liver.—Two important glandular appendages of the digestive tract, the liver and pancreas, will be described but briefly here. The liver (*hepar*), the largest gland in the body, weighs 2 to 4½ pounds (1,000 to 2,000 Gm.), averages 3½ pounds and forms one-fiftieth of the body weight in adults and one-twentieth to one-eighteenth in the newborn. It occupies large areas of the epigastric and right hypochondriac regions and a small area of the right lumbar region. The projection of its contour on the surface of the trunk may be defined thus: take point 1 in the right mammary line on the fifth rib, point 2 on the left mammary line in the fifth interspace and point 3 about 2 cm. below the tenth rib on the right lateral chest wall; a slightly concave line from 1 to 2 marks the upper (diaphragmatic) outline; convex lines from 2 to 3 and from 3 to 1 mark, respectively, the anterior free margin and the right side. The liver is somewhat lower in the erect than in the recumbent body and moves with the diaphragm in respiration.

What were formerly considered five lobes of the liver are now reduced to four; what was once called the caudate lobe is now the caudate process of the caudate lobe, this latter having been called the spigelian lobe formerly. The largest part of the liver is the right lobe, a lesser part the left lobe and the least parts the intervening quadrate and caudate lobes, these last two being configurations of the inferior (visceral) surface. Between the right and quadrate lobes are the gallbladder and its fossa; between the left and quadrate lobes is the umbilical fissure (lodging ligamentum teres); between the right and caudate lobes is the inferior vena cava and its fossa; between the left and caudate lobes is the fissure for ligamentum venosum. The fossae of the gallbladder and inferior vena cava form the right limb of the classic H; the fissures for ligamentum teres and ligamentum venosum form the left limb; the cross bar of the H is the porta hepatis (portal fissure), where the portal vein and the hepatic artery enter and the biliary system leaves the liver.

The so-called ligaments of the liver are of two kinds: (1) fibrous vestiges of the fetal circulation, (2) peritoneal derivatives of the ventral mesogastrium. Thus ligamentum teres from the umbilicus to the porta hepatis was the umbilical vein; ligamentum venosum was the sinus venosus, a large shunt from the umbilical vein across the portal vein to the inferior vena cava. The falciform ligament, the free border of which encloses ligamentum teres, is the prehepatic portion of the ventral mesogastrium, as in a sense is the coronary ligament, with its lateral expansion, the triangular ligament of each side. The posthepatic portion of the ventral mesogastrium is the lesser omentum (hepatogastric and hepatoduodenal ligaments), attached to the lesser curvature of the stomach and the superior part of the duodenum.

The passages conveying bile from the liver to the duodenum are the hepatic duct, common bile duct, cystic duct and gallbladder. Ducts from the right and left sides of the liver unite in the porta hepatis to form the *hepatic duct*, which passes down 1 to 1¼ inches (25 to 31 mm.) to join the cystic duct, whence it continues as the common bile duct.

Gallbladder.—The gallbladder (*vesica fellea*), with its cystic duct considered a diverticulum of the bile duct, is a reservoir about 3 inches (7.5 cm.) long, with a capacity of 1 to 1½ ounces (30 to 45 cc.). Its fundus (wide end) appears at the anterior free margin of the liver in relation to the abdominal wall at the tip of the ninth costal cartilage and in the angle formed by the costal margin and the lateral border of the rectus abdominis muscle, or again just medial to the midclavicular line (Fig. 13). Directed backward, upward and to the left it forms an S-shaped neck in the porta hepatis before continuing as the cystic duct. The peritoneum of the visceral surface of the liver usually includes the gallbladder, leaving the bladder surface attached to the fossa by areolar tissue. Sometimes the bladder is attached to the liver by a mesentery, or it may be deeply embedded in liver substance and its fundus may not appear at the free border of the liver. Constrictions in its walls may divide it into sacculations, or it may be divided longitudinally into two bladders, each opening into a hepatic duct. Again it may be connected directly by small hepatocystic ducts with the lesser bile vessels. Finally it may be absent, one or both hepatic ducts then being distended.

The cystic duct, usually half the caliber of the hepatic duct, is also slightly longer and takes an irregular course medially to open into the common bile duct. A redundancy of mucosa forming the spiral valve of Heister, found in the neck of the gallbladder, is continued into the cystic duct. Sometimes the cystic duct joins the right instead of the main hepatic duct. The right and left hepatic ducts may take long separate courses through the lesser omentum or farther, with a correspondingly long cystic duct and short common bile duct.

Common Bile Duct.—The common bile duct (*ductus choledochus*), about 3 inches (7.5 cm.) long and ¼ inch (6 mm.) wide, passes from the porta hepatis (1) through the lesser omentum with the portal vein behind and the hepatic artery to the left, (2) then beneath the superior part of the duodenum and (3) finally through the head of the pancreas (75 per cent of cases) or between the pancreas and the duodenum, where with the pancreatic duct it pierces the duodenal wall posteromedially and obliquely for ½ to ¾ inch (12 to 18 mm.). The two ducts run parallel, usually almost to the tip of the duodenal papilla, within which their common opening shows a dilatation, the ampulla of Vater. Circular and oblique fibers of smooth muscle at the lower extremity of the ducts form a sphincter (of Oddi), the action of which between periods of digestion appears to be the closing of the bile duct and causing of bile to accumulate in the gallbladder.*

Pancreas.—The pancreas, 5 to 6 inches (12.5 to 15 cm.) long, is shaped like a prone J with the left limb up and the hook to the right. It extends horizontally across the posterior abdominal wall through the epigastric and hypochondriac regions, its head and uncinate process (of Winslow) lying in the concavity of the duodenum, its prismatic body along the root of the transverse mesocolon and its tail against the spleen. The upper surface of the body, covered by peritoneum of the lesser sac, is part of the stomach bed; its lower surface, covered by peritoneum of the greater sac, lies above the duodenojejunal flexure; its posterior surface, without peritoneal covering, crosses the aorta and the left kidney and suprarenal gland. Surgical approaches, *e. g.*, to drain a pancreatic cyst, are three: (1) through the lesser omentum between the liver and stomach, (2) through the greater omentum between the stomach and transverse colon, (3) beneath the transverse colon through the root of the mesocolon. To expose the head of the pancreas, an incision is made through the peritoneum along the right margin of the descending part of the duodenum, which latter, with the ascending colon, is retracted to the left.

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* For thorough studies on the development of the ampulla of Vater and the sphincter of Oddi see Schwegler, R. A., Jr., and Boyden, E. A.: *Anat. Rec.* **67**, 441; **68**, 17 and 193, 1937.

The *major pancreatic duct* (of Wirsung) extends from the tail through the body and head of the pancreas to open into the duodenum with the common bile duct (*vide supra*). Since the pancreatic duct, bile duct and ampulla of Vater are each much wider than the common opening on the duodenal papilla, a gallstone may be so impacted in the ampulla as to allow bile to flow leftward in the pancreatic duct, with resulting acute pancreatitis (Opie). The *minor* or *accessory pancreatic duct* (of Santorini) is variable in size and site of duodenal junction, is usually small, receives a communication from the major duct and drains part of the head and uncinate process.

The uncinate process may form a *lesser pancreas*, connected to the main gland only by a duct; likewise, the tail may form a *divided pancreas*. An *annular pancreas*, extension of the head, may surround the descending part of the duodenum. Either major or minor duct may be larger or smaller than usual or more rarely absent, or there may be three pancreatic ducts opening into the duodenum. Aggregates of pancreatic tissue (accessory pancreases) may occur in the walls of the stomach, duodenum or jejunum or in Meckel's diverticulum. Diverticula of the duodenum, especially those involving the whole duodenal wall, are often attended with variations of the pancreas.

STRUCTURE OF THE DIGESTIVE TRACT

Muscular Walls.—There is a distinct gradient in the thickness of the musculature investing the digestive tract, its decrement being in the caudal direction.* The esophagus has two robust tunics of muscle, the inner circular and the outer longitudinal; the latter differs from similar muscle elsewhere in the tract by being as thick as, and often thicker than, the circular tunic. In the stomach are three more or less separate layers, the outer longitudinal, the middle circular and the inner oblique. The longitudinal layer is strongly developed in relation to the curvatures, especially along the lesser; the circular layer is complete for the entire stomach and is massive at the pylorus; the oblique layer is incomplete, being mainly distributed over the fundus. Then follow the three parts of the small intestine, each with complete but not robust inner circular and outer longitudinal muscle layers. Finally and caudally is the large intestine, the least muscularized part of the digestive tube. Its inner circular fibers form a complete tunic, but its outer longitudinal fibers are lacking except along three narrow bands, the taeniae, which join and form complete tunics only at the two extremities of the large bowel, *viz.*, at the appendix vermiformis and the rectum. Thus the cephalocaudal decrement of muscle in the digestive tract is exemplified most strikingly in the longitudinal layer.

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* The concept of a functional gradient in gastrointestinal activity has been developed by W. C. Alvarez in an extensive series of reports (*Am. J. Physiol.* **35** to **50**, 1914–19; *J. A. M. A.* **65**, 1915, and subsequent papers in these and other periodicals). Also see Alvarez: An Introduction to Gastroenterology, New York, Paul B. Hoeber, Inc., 1939.

In the first parts of the digestive tube there is also a short gradient of striated muscle. Thus, the walls of the pharynx are entirely of striated muscle, as is the uppermost part of the esophagus. The second fifth of the esophagus shows a mingling of striated and nonstriated muscle; from that level caudally throughout the digestive tract the musculature is without exception nonstriated.

Diverticulum Formation.—The foregut, from the pharynx to the duodenal papilla, has a remarkable capacity to produce important organs by budding or diverticulum formation. The lungs arise as ventral diverticula from a septal arrangement in the region of the pharynx and esophagus; the stomach is dorsally saccated; the liver develops from a ventral diverticulum of the duodenum; the pancreas is a fusion of a ventral and a dorsal bud from the duodenum; other diverticula of the duodenum are related to anomalies of the pancreas. The midgut has a much more limited capacity for budding; the cecum and appendix are sometimes cited as examples of diverticulum formation; Meckel's diverticulum is not strictly an intestinal bud but is a vestige of the vitellointestinal duct. The hindgut is usually devoid of organs or parts formed by budding. Thus the digestive tract expresses a distinct cephalocaudal gradient in diverticulum formation, with a caudal decrement in such activity.

The Digestive Mucosa.—The epithelium of the digestive tract, unlike the musculature, is given to sharp demarcation of types from one region to another. The mucosa of the esophagus is thickly stratified squamous epithelium. On its surface empty large ducts of esophageal glands, which latter, deeply lodged in the submucosa, are racemose and mucous. A distinct crenated line marks the level at which the mucosa of the esophagus ends and that of the stomach begins.

The lining of the undistended stomach appears as heavy, longitudinal folds or rugae, whose entire surface is mammillated. When the stomach distends, the rugae disappear, since they are in fact produced by redundancy of the mucosa; the mammillae, on the other hand, are retained as permanent configurations. When the mucosa is examined under low magnification (25 diameters), the mammillae are seen to be everywhere set with small polyhedral depressions, representing the openings of gastric glands. The columnar epithelium of the mucosa is elaborately evaginated through the lamina muscularis mucosa to form tubular glands within the submucosa. Of these glands three types are usually distinguished: (1) cardiac, (2) fundic, (3) pyloric. The *cardiac glands* (1), located near the esophageal opening into the stomach, are simple tubules lined with low columnar cells, the only function of which is said to be that of secreting mucus. The *fundic glands* (2), located in the fundus and body of the stomach, are long, tubular and lined by two varieties of cells: (*a*) the *chief cells,* polyhedral and forming a continuous wall of the tubule, are credited with producing pepsin and hence are called *peptic glands*; (*b*) the *parietal cells,* spheroid, deeper staining and located at irregular intervals between the chief cells and the basement membrane, are said to produce hydrochloric acid and hence are referred to by Langley as *oxyntic cells*. Bensley found that cells in the neck of the gland are modified chief cells and are concerned only with production of mucus. The *pyloric glands* (3), located in the pyloric antrum, are short but tortuous tubules lined with low columnar cells, the secretion of which is said to be free of pepsin. Starling called their secretion a chemical activator of the fundic glands, *i. e.*, a gastric secretin ot hormone.

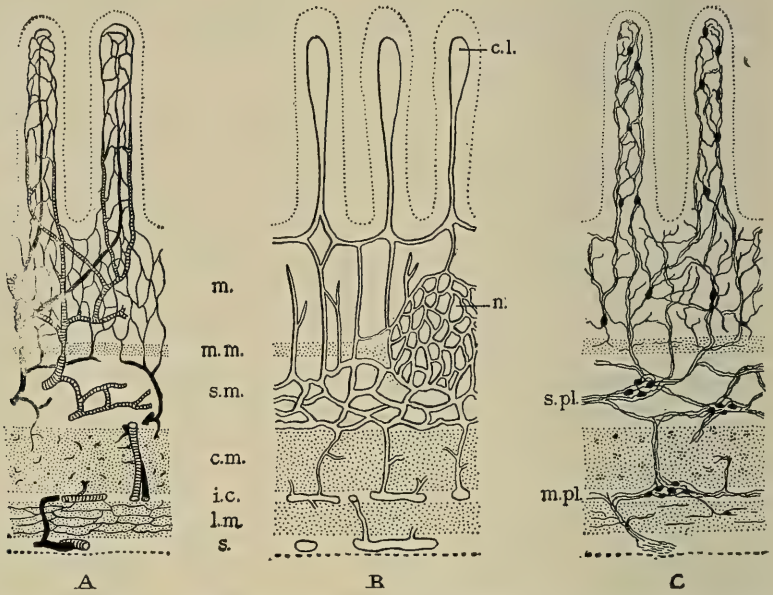

FIG. 19.—Diagrams of vessels and nerves of small intestine, three villi appearing as finger-like processes (Lewis and Stohr). At *A* the arteries are coarse black lines; the veins are shaded, and the capillaries are fine lines (after Mall). *B* shows the lymphatic vessels (after Mall). *C* shows the nerves in Golgi preparations (after Cajal): *m.* designates mucosa; *m.m.*, muscularis mucosae; *s.m.*, submucosa; *c.m.*, circular muscle; *i.c.*, intermuscular connective tissue; *l.m.*, longitudinal muscle; *s.*, serosa (peritoneum); *c.l.*, central lymphatic vessel; *n.*, lymph nodule; *s.pl.*, submucous plexus (of Meissner-Billroth); *m.pl.*, myenteric plexus (of Auerbach). (Reproduced from Morris' Human Anatomy, by permission of Dr. C. M. Jackson and The Blakiston Company.)

Within the small intestine are configurations which multiply the digestive-absorptive surface of the mucosa. Largest of these are the transverse ridges, the *plicae circulares* (formerly called *valvulae conniventes*), 2 inches (5 cm.) or less in length and $\frac{1}{8}$ inch (3 mm.) in width; their estimated total in the adult is 800 (Gundobin). These are permanent duplications of mucosa and submucosa, are set close together and are usually crescentic, involving one-half to two-thirds of the lumen; infrequently they form circles or spirals and may branch and anastomose. Absent in the duodenal antrum or "cap," they are largest in the lower part of the duodenum and upper part of the jejunum, whence they become smaller and finally disappear in the lower part of the ileum.

Other configurations greatly multiplying the surface mucosa are the *villi*, 0.5 to 0.7 mm. high, leaf shaped and very numerous in the duodenum and jejunum and cone shaped and scattered in the ileum. For the disposition of the blood and lymphatic vessels and nerves in relation to the villi and layers of intestinal wall, see figure 19. At the basal ends of the villi open short tubular *intestinal glands* (*crypts of Lieberkuhn*), in addition to which in the duodenum are the racemose *duodenal glands of Brunner.*

The mucosa of the entire small intestine is studded with small lymph nodules (*solitary glands*); that of the ileum, increasingly in its lower part, lodges *aggregate lymph nodules* (*Peyer's patches*). These latter, confined to the antimesenteric wall, are ovoid, ½ to 3 inches (1.2 to 7.5 cm.) in length and ¼ to 1 inch (1 to 2.5 cm.) in width, their length coinciding with the long axis of the ileum. Peyer's patches, 20 to 30 in number, may be the sites of multiple ulcers in typhoid fever and intestinal tuberculosis.

Within the large intestine the only conspicuous structures are the *semilunar folds,* crescentic ridges between haustra involving the whole intestinal wall. Plicae circulares, villi and Peyer's patches are absent. Solitary nodes and crypts of Lieberkühn are numerous; within these crypts and on the surface are large numbers of mucous "*goblet cells.*"

The vermiform appendix tends to become a fibrous cord with advancing age; always patent in infancy, the lumen is obliterated in about 50 per cent of persons over fifty years old. The appendix is called the "abdominal tonsil," because most of its wall is made up of a dense collection of solitary lymph nodes.

The interior of the rectum presents three obliquely transverse folds, *plicae transversales recti* (*valves of Houston*): the first at the left near the junction of the rectum with the sigmoid colon, often a site of constriction; the second at the right, largest and most constant, and 3 inches (7.5 cm.) from the anus; the third to the left, about 1 inch (2.5 cm.) below the second, and the least constant of the three. The valves of Houston correspond to the lateral flexures of the rectum and involve the entire rectal wall.

Developmentally the anal canal is formed by downward growth of the hindgut and upward growth of a skin pit, the *proctodeum,* the two being separated by the *proctodeal membrane.* This membrane normally disappears, its site being marked by an undulate white line, the *pectinate line of Hilton.* The anatomic and surgical significance of this line may be summarized as follows: 1. It is a transition zone between the columnar epithelium of the intestine and the squamous epithelium of the skin. 2. Here the internal sphincter (smooth muscle) is followed by the external sphincter (striated muscle); between the two is a zone of weakness through which an abscess of ischiorectal fossa may rupture into the rectum and establish the inner extremity of a fistula. 3. At this line areas of autonomic and spinal innervations come together. 4. Here areas of portal and caval venous drainage overlap, the superior hemorrhoidal vein going to the portal *via* the inferior mesenteric and the middle and inferior hemorrhoidal to the caval *via* the pudental and hypogastric. 5. Here areas of lymph drainage overlap, those above the line passing to the pelvic nodes and those below to the subinguinal nodes. 6. Along this line are the *anal valves,* cusplike folds connecting parallel *rectal columns* (of Morgagni) and covering the *rectal sinuses,* which latter, opening upward, may be torn by scybala with a resulting fissure *in ano.*

The epithelium of the liver and that of the pancreas require brief attention. The liver epithelium is best described in terms of the vascular units of liver. These units, or *lobules,* are polygons 1 to 2 mm. in section, separated by interlobular connective tissue, in which are the terminal branches of the hepatic artery, portal vein and bile ducts. The portal branches surrounding a lobule are termed *interlobular veins;* these give off hepatic capillaries, directed toward the center of the lobule, where they unite to form the *central* or *intralobular vein.* Numbers of these latter form a *sublobular vein;* numbers of these in turn form the hepatic vein. The epithelial cells of the liver are arranged as columns in the spaces between the hepatic capillaries; within these columns arise the bile capillaries, which pass to the periphery of the lobule and unite to form first divisions of the bile ducts. The liver is enclosed by a stout connective tissue capsule (of Glisson), sheaths of which are carried in with the vessels at the porta.

The lobules of the pancreas are loosely assembled like those of the salivary glands and are similar to these latter in the arrangement of secretory tubules and ducts. The tubules are lined with low cylindric cells, with deeply placed nuclei and marginal collections of granules. Centered at the base of the tubule are spindle-shaped *centroacinar cells.* Between the gland acini of each tubule are cords of cells, not glandular in structure and not connected with ducts. These are the *islands of Langerhans,* known to produce an internal secretion, *insulin,* of great importance in carbohydrate metabolism. These islands are said to number 200,000 to 1,750,000 (Maximow-Bloom). Their insufficiency leads to diabetes mellitus.

THE NERVE SUPPLY OF THE DIGESTIVE TRACT

Sensory fibers from the digestive tract reach the central nervous system *via* vagus or sacral nerves (craniosacral autonomic system) or *via* splanchnic or hypogastric nerves (thoracolumbar autonomic system). While it is common knowledge that there are visceral sensations, *e. g.,* hunger, colic and burning, yet cutting the intestine is said to produce no pain at all.

In general the motor supply to the digestive tract consists of the craniosacral autonomic system for acceleration and the thoracolumbar for inhibition. To this rule, however, there are exceptions. In the filling-emptying mechanism of the stomach the thoracolumbar system inhibits the activity of the stomach walls but keeps the pylorus in tonic contraction; thus it controls the filling mechanism. With the stomach reaching a certain limit of distention, sensory fibers set up a vagus reflex, whereby the pylorus is relaxed and the walls are contracted; thus the cranial autonomic system controls the emptying mechanism.* Much the same formula holds for the rectum: the thoracolumbar system *via* the hypogastric nerves relaxes the rectal walls and keeps the sphincter contracted, while the sacral autonomic system relaxes the sphincter and contracts the walls, the external sphincter being normally under voluntary control. (For accounts of these reflexes in terms of neurons see Wilkinson, 1935, and De Garis, 1938.)

From the foregoing description it appears that the digestive tract is operated by the antagonistic action of the two autonomic systems. A remarkable imbalance in their action is exmplified in megacolon (Hirschsprung's disease), where the sigmoid colon is enormously distended and inactive. Removal of the inhibiting nerves (thoracolumbar) by ganglionectomy and ramisectomy is reported to give much relief in such cases (Judd and Adson, 1928).

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* For divergent views on the mechanism of gastric evacuation see Cannon, W. B., *The Mechanical Factors of Digestion*, New York, Longmans, Green & Co., 1911; McSwiney, B. A.: *Physiol. Rev.* **11**, 478, 1931; Thomas, J. E., Crider, J. O., and Mogan, C. J.: *Am. J. Physiol.* **108**, 683, 1934; Crider, J. O., and Thomas, J. E.: *Am. J. Digest. Dis.* **4**, 295, 1937.

DEVELOPMENTAL SEQUENCES

Where the developmental history of striated muscle is customarily read off from its nerve supply, that of the digestive tract is by no means so clearly documented there. Rather, one must look to the arteries. Thus, the first branch of the abdominal aorta to the digestive tract, the *celiac artery* (*axis*), supplies the abdominal portion of the *foregut*, this comprising the stomach, the duodenum as far as the duodenal papilla, the liver and the pancreas; the second branch, the *superior mesenteric artery*, supplies the *midgut*, which includes the rest of duodenum, the jejunoileum, the cecum, the ascending colon and the right two-thirds of the transverse colon; the third branch, the *inferior mesenteric artery*, supplies the *hindgut*, *i. e.*, the rest of transverse colon, the descending and the sigmoid colon and the rectum. These three vascular units of the gut are also developmental and in a sense functional units.

Before a discussion of developmental sequences in detail, one important process, applying to mesothelial contacts in general, should be recounted. Where two surfaces, *e. g.*, of peritoneum, are for a time in contact and do not from peristaltic or other activities move on each other, the two surfaces adhere, and eventually their mesothelium as such degenerates, leaving the parts held together by areolar tissues, with part-to-part confluence of peritoneum along their boundaries. This process of *peritoneal fixation* will be found to play a decisive role in establishing definite positions, in both hepatogastric and intestinal regions of the abdomen.

In the early stages the digestive tube is suspended from the midline of the dorsal body wall by a continuous mesentery, and the foregut is suspended from the midline of the ventral body wall by a mesentery, in part of the free (caudal) margin of which is enclosed the umbilical vein. The stomach becomes saccated in the dorsal mesentery (here the *dorsal mesogastrium*); into this develop also the spleen and the pancreatic buds, while into the ventral mesentery (*ventral mesogastrium*) grows the liver. This organ increases rapidly in size and fills the upper part of the abdomen, extending ventrally to the umbilicus. Neglecting here the complicated invasions and shifts of vascular channels caused by the liver, suffice it to say that the ventral mesogastrium and *septum transversum* (fundament of the diaphragm) are so far outgrown by the liver that when the septum gives place to the diaphragm a "bare area" is left with the diaphragm and liver in direct contact, the peritoneal reflections along this area being the *coronary ligament*.

During this over-growth of the liver the stomach turns clockwise through 90 degrees to present its saccated dorsal border (*greater curvature*) to the left, its concave ventral border (*lesser curvature*) to the right, its left surface (and left vagus branches) ventrally and its right surface (and right vagus branches) dorsally. During this change the spleen and pancreas with attached dorsal mesogastrium are extruded to the left; by peritoneal fixations of parts of the dorsal mesogastrium the pancreas becomes retroperitoneal and the *lienorenal ligament* is formed; this and the *gastrolienal* *ligament* are in sum the dorsal mesogastrium at this level of the greater curvature. Likewise from the lesser curvature to the ventral body wall the *lesser omentum* and *falciform ligament* are in sum the ventral mesogastrium. Behind the liver, lesser omentum and stomach a portion of the general peritoneal sac is pinched off by the over-growth of the liver and the turning of the stomach, so that it communicates with the general sac only at the free margin of the lesser omentum. The sac so isolated is the *omental bursa* (*lesser sac*), and its communication is the *epiploic foramen* (of Winslow).

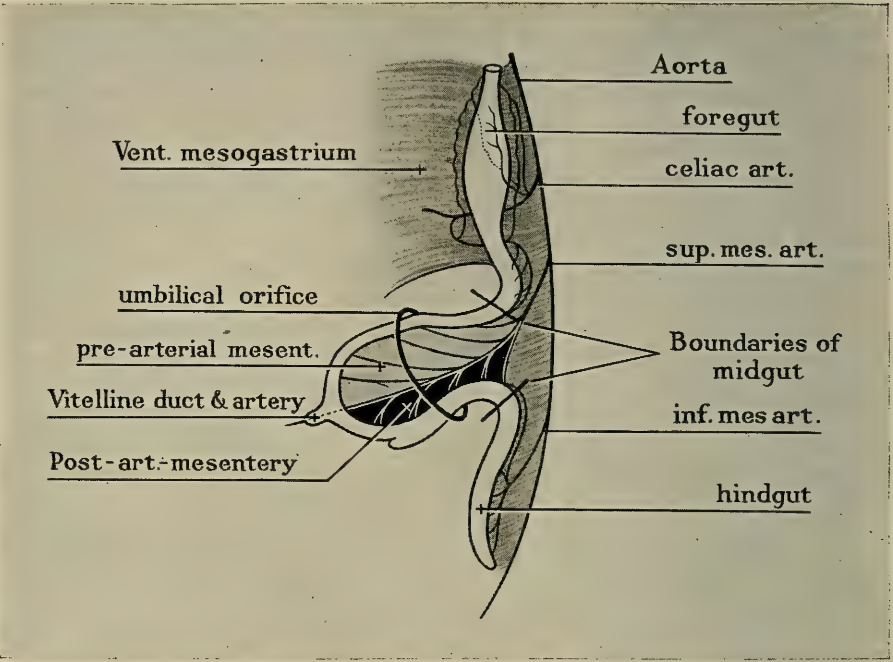

FIG. 20.—Lateral diagram of digestive tract at fifth week. The midgut loop protrudes into the umbilical cord; the *umbilical orifice* here and in subsequent figures is represented by a heavy circle. Crossing lines denote upper and lower limits of the midgut loop. The superior mesenteric artery passes through the dorsal mesentery from the aorta to the vitelline duct. The *prearterial mesentery* is shown in gray; the *postarterial mesentery* in black, a marking device used throughout this series of diagrams (Figs. 20 to 27). The cecal bud has recently appeared. The foregut is suspended from the ventral wall by the *ventral mesogastrium.* The foregut, midgut and hindgut are seen to be vascular units in the sense of having separate supplies from the aorta. (After Dott.)

Whereas the part of the dorsal mesogastrium at the level of the spleen is extruded to the left, the part from the lower levels of the greater curvature is extruded downward, forming the *greater omentum,* the extruding space within it being the *inferior recess* of the omental bursa. The greater omentum passes caudally over the transverse colon and small intestine; finally by a series of peritoneal fixations it becomes attached to the transverse colon and mesocolon. At times its cavity becomes obliterated by fixation, in which case a definitive fold of peritoneum passes from the greater curvature of the stomach to the transverse colon (*gastrocolic ligament*). The *superior recess* of the omental bursa is the space directly isolated by the liver; it passes upward over the caudate lobe, the only part of the liver covered by peritoneum of the omental bursa. Such in brief are the developmental changes in the gastrohepatic region.

The aforementioned changes in the foregut and its appendages are concurrent with, and in a sense causative to, certain mechanical alterations attending rotation of the midgut. The following account of intestinal rotation and the anomalies incident thereto is based on the excellent report of N. M. Dott (1923), and figures 20 to 27 are black and white arrangements of his illustrations, here reproduced by permission. In figure 20 is shown a side view of the abdominal part of the digestive tract at the fifth week.

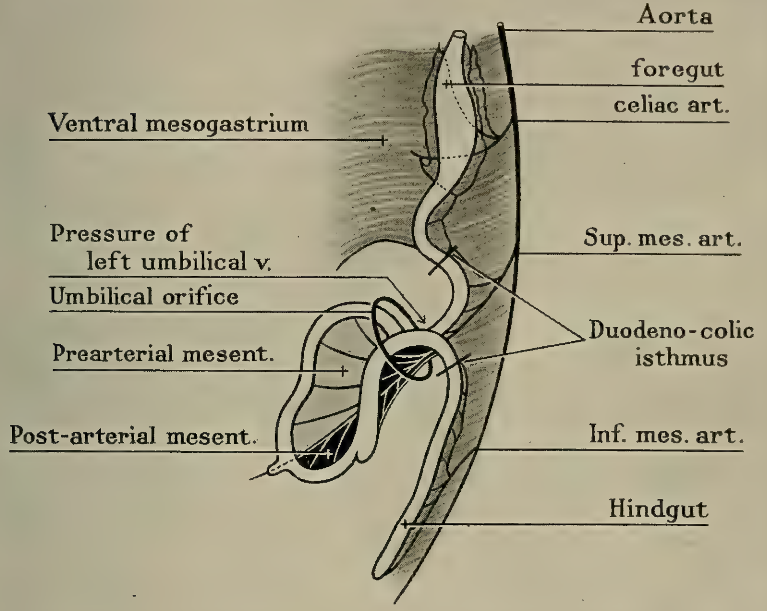

FIG. 21.—Lateral diagram of the digestive tract at or about the eighth week. The first stage of rotation is in progress with the *prearterial segment* being depressed and forced to the right by the umbilical vein and right lobe of the liver; the *postarterial segment* is undergoing a compensatory upward thrust. The narrow pedicle of the loop is the *duodenocolic isthmus*, with the superior mesenteric artery passing through it. (After Dott.)

Before this time the stomach has become saccated into the dorsal mesogastrium, and the duodenum has been thrust to the right and fairly fixed by the growth of the pancreas into the dorsal mesentery. The hindgut at its upper end is held in place by a thickened mesentery, or "*retention band*" (Frazer and Robbins, 1915), attached to the condensed tissue about the root of the superior mesenteric artery. Since this band does not grow with the gut and the mesentery, it serves to "hitch up" the midgut and the hindgut, forming a bend, the *colic angle*, at their point of union. Thus, two fixed points, the colic angle and duodenum, are brought close together, producing the *duodenocolic isthmus*, from which depends the entire midgut loop. Since the liver and midgut, both growing rapidly, soon exceed the space available in the abdomen, the midgut is extruded into the root of the umbilicus as a physiologic hernia, at the apex of which are the vitellointestinal duct and the termination of the superior mesenteric artery. The midgut loop still lies in the sagittal plane; its part cephalad to the artery is termed the *prearterial segment* (with *prearterial mesentery*), and that caudad to the artery is termed the *postarterial segment* (with *postarterial mesentery*—black areas in figures 20 to 27). During the fifth week the cecoappendix appears as a bud on the postarterial segment.

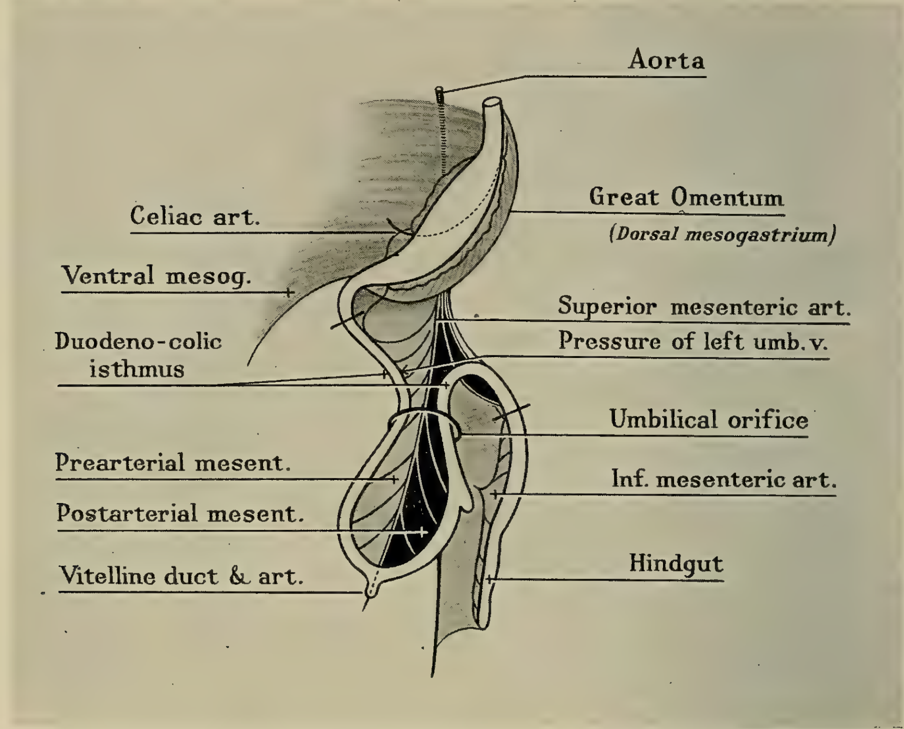

FIG. 22.—Ventral diagram of digestive tract in the same stage as that shown in figure 21. The *prearterial segment* is at the right; the *postarterial segment* at the left. In definitive conditions of "nonrotation" these relations are maintained. (After Dott.)

First Stage of Rotation (Fig. 21, side view; Fig. 22, front view).—The first stage of rotation takes place between the fifth and tenth weeks, while the midgut loop is still in the umbilicus. During this time the right lobe of the liver and the umbilical vein grow down and press on the prearterial segment of the midgut loop near its base, carrying the gut caudally and to the right. Thus the prearterial and postarterial segments are for a time side by side in the narrow umbilical orifice; eventually the postarterial segment is displaced cranially. Since the prearterial segment and its mesentery grow much more rapidly than the postarterial parts, the superior mesenteric artery becomes relatively closer to the postarterial segment. Also this latter, as to the cecum and adjacent colon, increases in thickness, forming a postarterial swelling.

Second Stage of Rotation (Fig. 23).—At the tenth week the midgut loop returns to the abdominal cavity. But the narrow umbilical orifice does not admit passage of the entire hernial mass at one time; the enlarged cecum acts as the chief obstruction and is the last to leave the hernial sac (Mall, 1898, and Frazer and Robbins, 1915). The first part to enter the abdomen is the prearterial segment, in continuity, basal end first. The cecum and adjoining ileum and colon, while still in the umbilical cord, serve to hold the termination of the superior mesenteric artery, so that during the return of the prearterial segment the artery is suspended across the abdomen from the aorta to the umbilicus.

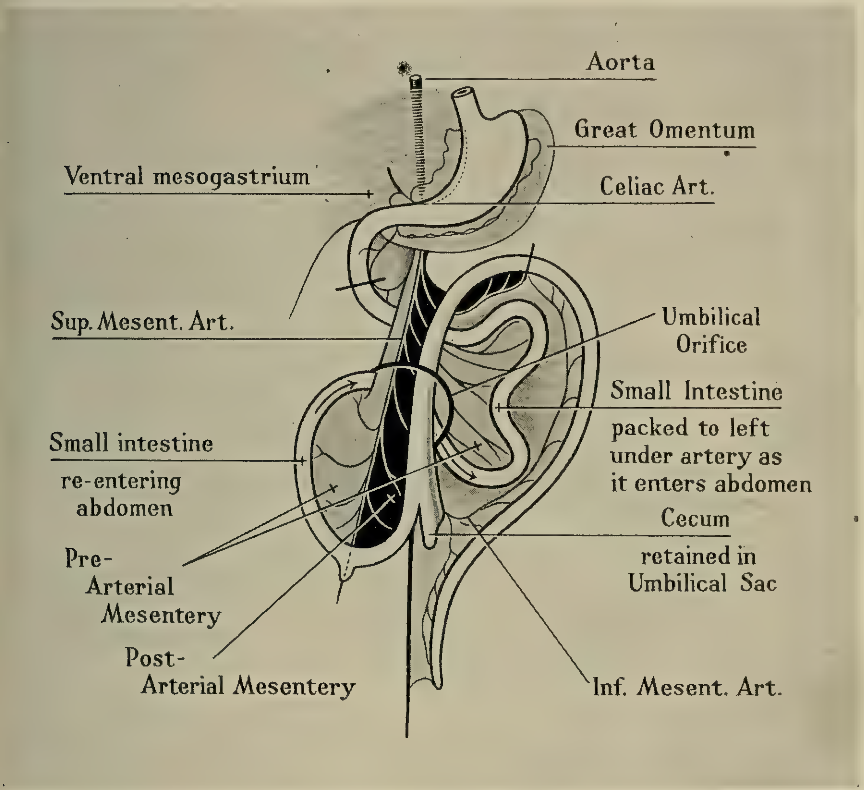

FIG. 23.—Ventral diagram of digestive tract at the tenth week. The critical second stage of rotation is in progress. The *prearterial segment* and *mesentery* have far outgrown the *postarterial segment* in length; however, the latter has increased in thickness in relation to the cecum and colon and still lies in the umbilical cord, serving to hold the superior mesenteric artery suspended across the abdomen. Loops of the prearterial segment (small intestine) have entered the abdomen behind and to the right of the superior mesenteric artery and are filling the available space at the left, pushing the colic angle upward and the hindgut with its mesentery leftward. (After Dott.)

The small intestine enters the abdomen on the right side of the artery, and as coils accumulate in the abdomen other entering coils push them behind the outstretched artery into available space at the left. This leftward thrust of the intestinal coils pushes the hindgut and its mesentery away from the midline and folds them backward and to the left, at the same time displacing the colic angle farther upward. The last returning coil of ileum carries the superior mesenteric artery with it, and finally the cecum and adjacent colon are reduced. The cecum is now free near the umbilicus and anterior to the small intestine and mesenteric artery; however, the colon begins to straighten and carries the cecum with it to the right and upward, the colon lying across the pedicle of the intestinal mass and mesenteric artery and the cecum lodging beneath the liver. Subsequent linear growth of the colon causes the cecum to reach its definitive position in the right iliac region. Figure 24 depicts completion of the second stage of rotation. From this it is seen that the net result of the second stage of rotation is a counterclockwise turn through 270 degrees

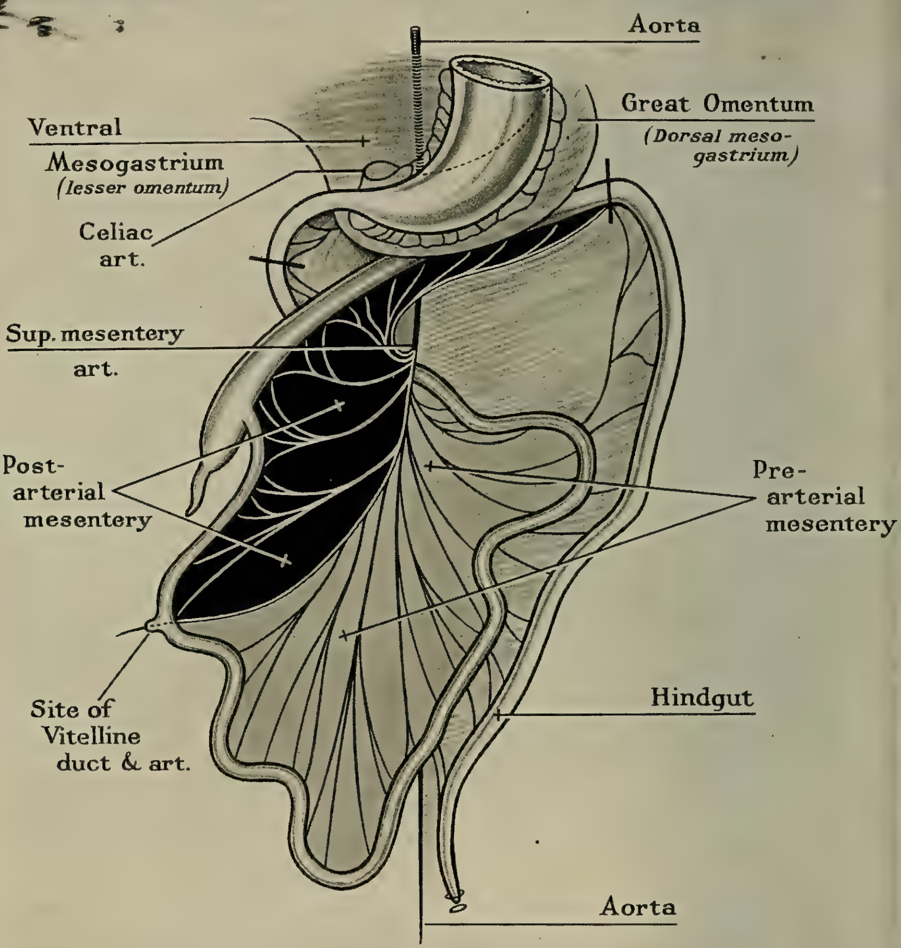

FIG. 24.—Ventral diagram of digestive tract at or about the eleventh week. Rotation of the midgut loop is complete, with return of the cecum to the abdomen, where it now occupies the right lumbar region. From its original sagittal plane the midgut loop has turned *counterclockwise through 270 degrees* about the superior mesenteric artery as an axis. Except for further descent of the cecum, fixation of the ascending and the descending colon and fusion of the jejunoileal mesentery, the definitive arrangement of viscera has been attained. (After Dott.)

from the original midline position of the midgut, the axis of rotation being the superior mesenteric artery. As a result the duodenum is drawn behind the root of the artery and the colon is left in front of the artery and duodenum.

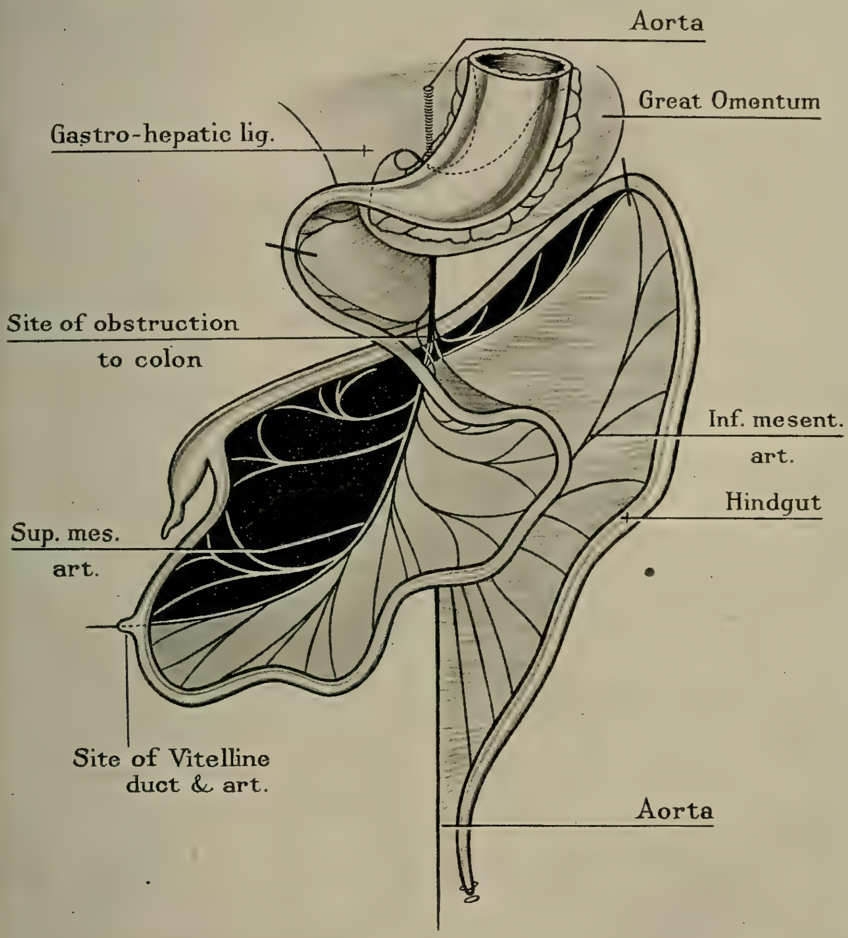

Fig. 25.—Ventral diagram showing reversed rotation of the midgut loop, which has turned *clockwise through 90 degrees* from the original sagittal plane. This rotation has brought the colon behind the superior mesenteric artery and the duodenum in front of it. Other visceral relations are normal, though the anterior and posterior surfaces are reversed. This figure is from Dott's Case I, in which surgical intervention was required because of volvulus of the cecum and ascending colon. (After Dott.)

Third State of Rotation.—While some further descent of the cecum may occur, this stage is essentially one of peritoneal fixations. The duodenum in the retroarterial position loses its mesentery and posterior peritoneum and secondarily becomes fixed to the hepatic flexure and transverse colon. The superior mesenteric artery is directed to the right iliac region by the descent of the cecum, and during the twelfth week the mesentery bearing the artery fuses obliquely from above downward against the posterior abdominal wall along the line of the artery. The prearterial mesentery is left free as the mesentery of the jejunoileum, and a part of the postarterial mesentery remains for the terminal part of the ileum and transverse colon; other parts of the postarterial mesentery normally disappear by peritoneal fixation. Where the cecum and ascending colon have a mesentery, then this plus the mesenteries of the terminal ileum and transverse colon represent the complete persistence of the postarterial mesentery.

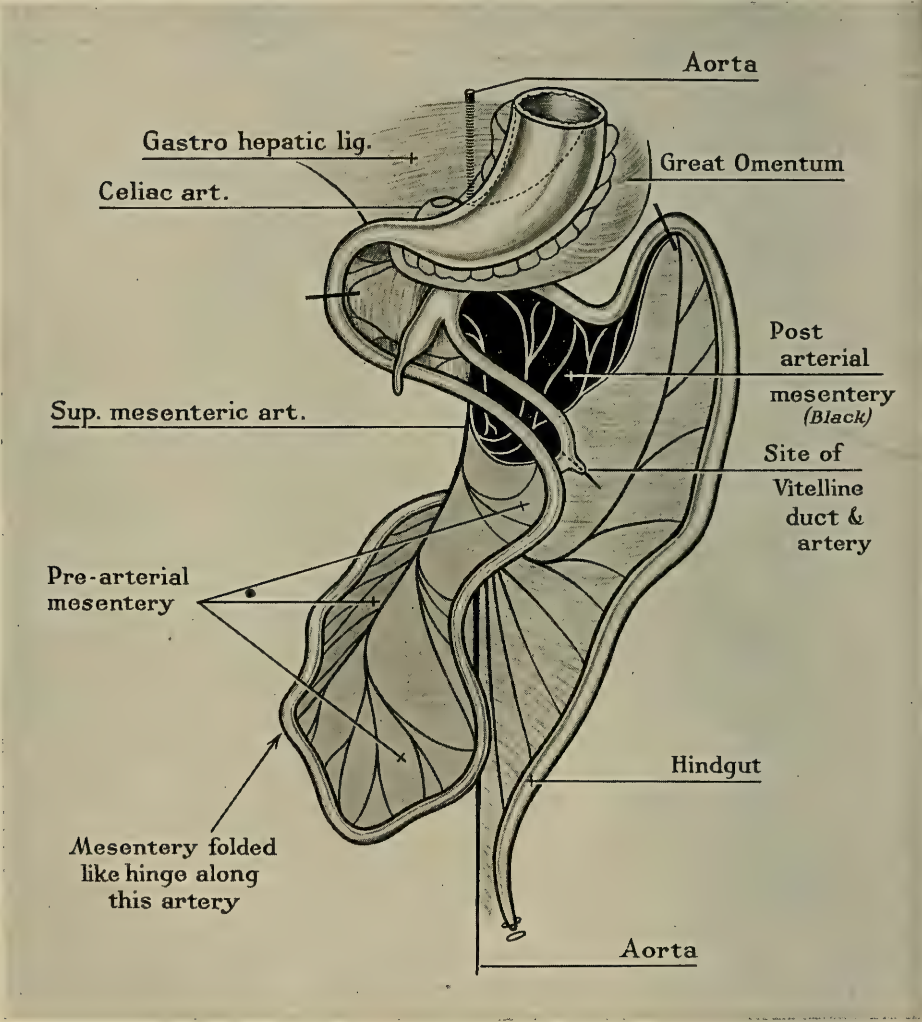
Aorta
Gastro hepatic lig.
Great Omentum
Celiac art.
Post arterial mesentery (Black)
Sup. mesenteric art.
Site of Vitelline duct & artery
Pre-arterial mesentery
Hindgut
Mesentery folded like hinge along this artery
Aorta

Fig. 26.—Ventral diagram showing malrotation of midgut loop. The *prearterial segment* has rotated *clockwise through 90 degrees*, while rotation of the *postarterial segment* has been arrested. The mesentery is folded hingelike along the superior mesenteric artery. (After Dott.)

Errors of Rotation (Figs. 25 to 27).—**Second Stage.**—Errors are confined largely to the second stage of rotation, and according to Dott are mainly due to a lax or large umbilical orifice, allowing the midgut to return to the abdomen in some sequence other than that described. These errors fall into three groups:

Group 1. Nonrotation of Midgut Loop.—The cecum returns first, carrying with it the colon, the lower loop of the ileum and the superior mesenteric artery. The small intestine follows but does not pass behind the artery; rather, it displaces the artery and the large intestine to the left, where a pelvic or left iliac cecum receives the ileum from the right.

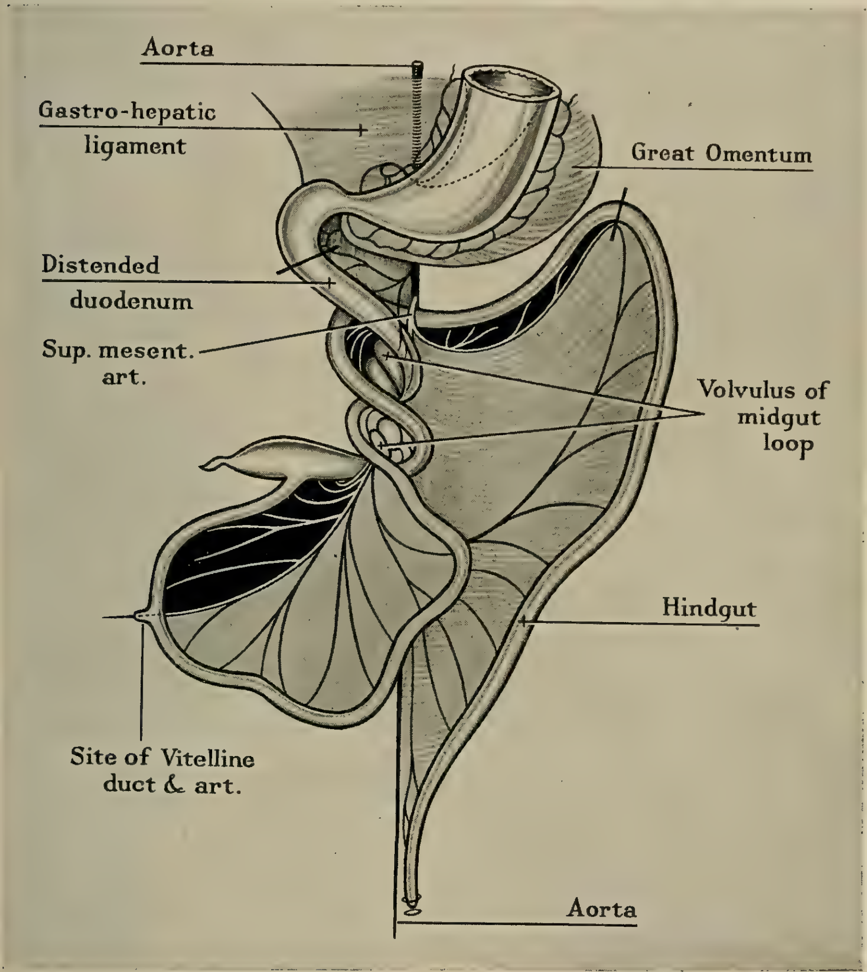

FIG. 27.—Ventral diagram showing volvulus of nonrotated midgut loop. There has been a *clockwise turn of 450 degrees* from the original sagittal plane, or *two complete turns* (*720 degrees*) from the normal position. This figure is from Dott's Case II, the outstanding feature of which was acute duodenal obstruction. (After Dott.)

Group 2. Reversed Rotation of Midgut Loop.—The midgut loop rotates clockwise through 90 degrees, with the transverse colon crossing behind the superior mesenteric artery and the duodenum crossing in front of it (Fig. 25). In this case the whole midgut loop is suspended by a narrow pedicle, the duodenocolic isthmus.

Group 3. Malrotation of Midgut Loop.—The superior mesenteric artery with the last ileal loop may be reduced first, whence follow the prearterial and postarterial segments, both passing in front of the artery. The cecum may take a subpyloric position, with all of the small intestine suspended by a narrow pedicle, the duodenum and terminal part of the ileum lying side by side. In other cases the prearterial segment occupies the right side, as in nonrotation, and the postarterial segment rotates normally but its fixation on the right side is prevented by the prearterial segment.

Third Stage.—Too early fixation of the cecum or failure of growth of the colon causes the subhepatic and the right lumbar location of the cecum. Lack of fixation or excessive growth of the colon accounts for the pelvic location. The "mobile proximal colon" and "floating ileocolic segment" are likewise produced by deranged fixation. The various errors of rotation described are, of course, attended by errors of fixation. Volvulus, stricture and other hazards arising from rotational errors and abnormal fixations do not require discussion here.

In striving for some measure of completeness I can have achieved little more than a bleak citation of facts; also from sheer necessity a great many facts have been omitted. For fuller and more significant treatments of the digestive tract, a list of references is here appended, with attention directed especially to studies on the living body.

For figure 19, taken from Morris' Human Anatomy, I am much indebted to Dr. C. M. Jackson and The Blakiston Company. All other illustrations were made under my direction by Mr. E. F. Hiser, Oklahoma City. Figures 20 to 27 were arranged from the report by Mr. N. M. Dott, Edinburgh. To him my debt is great.

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CHAPTER III

THE INTERPRETATION OF GASTROINTESTINAL TRACT PAIN

With the advent of newer and more "scientific" diagnostic procedures, there is a growing tendency today for the physician to turn away from the detailed examination of the patient's own story as the most direct means of establishing a diagnosis. Too frequently "complete" gastrointestinal studies are ordered for a patient with digestive tract symptoms, without any adequate evaluation of the symptoms of which he complains. Pain originating in the alimentary tract is one of the commonest complaints encountered in the practice of medicine and when properly assessed will almost invariably lead to a correct diagnosis or to an intelligent rather than a routine search for the underlying cause. A careful anamnesis, therefore, must remain as a *sine qua non* in the diagnosis and the treatment of digestive disorders.

For a correct utilization of the word "pain," it is essential to employ it in its broadest sense: namely, that of any uncomfortable sensation arising from a disorder in function of the alimentary tract. Although secretory disorders undoubtedly form the basis of gastric or intestinal symptoms, the immediate origin of digestive tract pain in a neuromuscular disturbance. Such disturbances are fundamentally motor, are more or less localized, depending on the nature of the morbid process, and are mediated, for the most part, by the fibers of the autonomic nervous system or by the intrinsic motor mechanism of the gastrointestinal apparatus. In essence they are associated with a state of increased smooth muscle tension at a given level of the digestive tube and may be initiated by a localized gastrointestinal pathologic process, neighboring disease or excessive stimulation of parasympathetic or sympathetic fibers. They may be reproduced by cholinergic drugs, such as beta-acetylmethylcholine in the case of parasympathetic over-stimulation, or by sympathomimetic drugs, such as epinephrine. When due to parasympathetic disturbances, they may be blocked by atropine derivatives. The nitrites or calcium preparations frequently afford dramatic though transient relaxation of smooth muscle spasm associated with over-activity of either portion of the autonomic nervous system, with corresponding relief of the unpleasant symptoms.

The sensory disturbances incident to gastrointestinal disorders are undoubtedly carried over autonomic fibers supplying various levels of the gut and distributed along spinal segments, to be experienced as "referred pain." This interesting clinical phenomenon was originally well described by Ross and subsequently investigated in a series of classic studies by Head and Mackenzie. Except for the classification of important details, little has been added to the original concept of these brilliant clinicians by numerous subsequent investigators. A careful analysis of the diagnostic and therapeutic aspects of digestive tract "referred pain" will constitute the basis of this chapter.

As already suggested, the term "pain" must be employed in its least restricted sense. To the patient it will imply such sensations as distress, discomfort, colicky pain, ache, cramps, burning, hyperacidity, fulness, hunger sensations and the like. Again, there exists a vast difference in patients as to the apparent severity of a given sensation. The actual threshold for pain varies tremendously in given individuals, similar experiences causing subjective reactions which vary from agonizing pain to slight discomfort. Such variations in individual sensitivity are well recognized by experienced clinicians, but must be properly evaluated in order to obtain an accurate estimation of the underlying cause. Indeed, marked variations in subjective complaints may exist in a given patient and appear to be conditioned by emotional stress and strain, fatigue, depletion, intercurrent infection and other similar factors. Under such circumstances, it is obvious that even the most accurate history demands experience and skill for proper interpretation. Fortunately, however, referred pain possesses one important characteristic which is of sufficient constancy to be of supreme diagnostic importance: In the vast majority of instances, uncomfortable sensations arising from different levels of the alimentary tract tend to be felt at fairly constant levels and, in many instances, at fairly constant points. As a rule, on close questioning a patient will be able to demonstrate digitally the exact location of his painful sensations or the point where his pain is most intense. Such a maneuver should constitute an invariable part of a routine physical examination.

As a result of clinical and experimental observations, it is possible to present the following established facts in regard to digestive tract pain: For the most part, gastrointestinal pain is referred to the midline in front. If the point of stimulation is sharply localized, is fixed or is of small caliber, it can be stated that the localization of pain is relatively very sharp and distinct. When a violent disturbance is taking place, like that in acute intestinal obstruction, or when the morbid process is causing symptoms in a person with a very low sensory threshold, the distribution of pain will tend to be zonal or beltlike, although the segmental localization will persist. As a general tule, because of the larger caliber of the colon, pain there tends to be less intense than that in the small intestine.

In the esophagus, unpleasant sensations for the most part tend to be referred under the sternum at levels corresponding roughly to the level of origin of the underlying disease. Thus, a lesion in the upper third of the esophagus will usually cause discomfort at the midline under the upper third of the sternum, while an ulcer or stenosing lesion near the cardiac orifice will cause low substernal pain. One can usually predict with accuracy the approximate site of esophageal disturbances. Certain aberrant or atypical points of reference are worthy of mention. In some persons esophageal disturbances at any level cause pain to be referred only to the suprasternal notch. A small group of patients refer pain from esophageal disease to the back only, with a tendency to localize this sensation at the level of the seventh cervical vertebra, the third or fourth dorsal vertebra or the seventh dorsal vertebra as the upper, middle or lower esophageal region is stimulated. Another extremely important variation is that occasionally encountered in patients with esophageal ulcer or with symptoms due to the localized gastritis associated with a small diaphragmatic hernia. Not too infrequently these patients complain not only of low substernal pain or tightness, but of a distinct radiation to the left shoulder and arm entirely comparable to that associated with coronary heart disease. This latter manifestation provides a difficult diagnostic problem, but the realization that esophageal disease or disease of the cardiac end of the stomach can accurately mimic attacks of angina pectoris will occasionally result in a correct interpretation of a patient's difficulties.

Gastric pain is almost invariably located high in the epigastrium. When due to a sharply localized disturbance, such as an ulcer, or to spasm of the cardiac or pyloric sphincter, the resulting referred pain is usually well localized to a small area below the xiphoid process or in the upper part of the epigastrium. A diffuse process, such as gastritis, however, as a rule causes a much more diffuse type of epigastric distress. Irritation of the first portion of the duodenum also results in the production of pain referable to the epigastrium, usually at a point in the midline and about one-third of the distance between the tip of the xiphoid process and the umbilicus. It is usually sharply localized. A zonal distribution may occur, and again it is to be noted that pain in the back may accompany the anterior abdominal pain associated with gastric or duodenal pathologic processes. This latter phenomenon is extremely important and is borne out by clinical and experimental observations. When it occurs, the back pain associated with gastric and duodenal lesions is typically centered at the level of the eighth to the tenth dorsal vertebra. Rarely, such pain may be the *only* clinical expresion of a duodenal ulcer, a fact attested by few writers.

Disturbances in the middle and the lower part of the duodenum are definitely the cause of referred pain low in the epigastrium or high in the umbilical area, a level distinctly lower than that usually mentioned by patients suffering from duodenal ulcer. Such localization of pain is of real diagnostic importance, as the less common peptic ulcers and rare malignant growths that occur in the lower portions of the duodenum are frequently missed by routine roentgenologic measures. If, however, a careful history reveals the fact that pain at the midline of the lower part of the epigastrium is the outstanding symptom, the attention of the roentgenologist may be directed toward a search for a lesion low in the duodenum or at the duodenojejunal junction, with a reasonable chance of success. Back pain at the level of the tenth to the twelfth dorsal segment is not uncommon in association with lower duodenal lesions. As pathologic lesions, either benign or malignant, are uncommonly found in this part of the intestinal tract, it is important to remember that they produce rather characteristic localization of symptoms. Peptic ulcer, leiomyosarcoma, adenocarcinoma and the like may occasionally be diagnosed thus.

The remainder of the small intestine, when disturbed, characteristically refers its pain to a fairly narrow zone, which starts about 1½ to 2 inches (3.8 to 5 cm.) above the umbilicus and extends downward a similar distance below this anatomic landmark. Except where the underlying process is diffusely scattered throughout the intestine or where the disturbance is extremely violent, midline localization of the pain is the rule. Acute enteritis and lead colic are examples of a diffuse involvement of the small bowel, and characteristically produce rather diffuse zonal pain in the umbilical segment. Partial intestinal obstruction due to a Meckel's diverticulum, a benign or malignant neoplasm of the jejunum or ileum, hyperplastic ileal tuberculosis, regional ileitis, ileal ulcer, mesenteric adenitis and the various acute small bowel emergencies associated with a volvulus, constricting bands, intussusception and the like, all are characterized by umbilical pain.

This may be sharply localized close to the midline, zonal or present chiefly in the back, at the first to the third lumbar level. As a rule, the lower the position of the lesion in the small bowel, the lower will be the umbilical pain. Unfortunately, this is not constantly true, and one is therefore limited to a suggestion of disease of the small intestine when periumbilical pain is encountered. Because of the relative infrequency of discrete jejunal or ileal lesions, it is important to emphasize the diagnostic importance of such a localization of pain. This is particularly true because of the fact that here, too, routine x-ray examinations leave much to be desired- Newer methods, however, permit a careful and fairly satisfactory examina. tion of the jejunum and ileum, if the clinician is wise enough to suggest to the roentgenologist that he suspects small bowel disease.

Ileocecal disease will usually cause lower umbilical pain because of the tendency of such pathologic processes partially to obstruct the terminal part of the ileum. Clinical and experimental observations are in agreement that a disturbance in the terminal part of the ileum just proximal to the ileocecal valve, such as may occur in "terminal" ileitis or ileocecal tuberculosis, will cause pain localized in the lower part of the umbilical region, usually to the right of the midline, in the direction of McBurney's point.

The localization of pain due to inflammatory reactions in the appendix is typically over McBurney's point, halfway between the umbilicus and the right anterior iliac spine. As pointed out in numerous clinical articles on this condition, appendiceal pain frequently may be located elsewhere, but such atypical reference is undoubtedly due to fixation of the organ in a retrocecal position or to peritoneal inflammation and resulting modification of pain. It is of interest, however, to note that pain produced experimentally by distention of the cecum exactly at the ileocecal valve shows a tendency to spread toward the epigastrium or even to appear in what might be termed a left McBurney localization, a radiation or reference not infrequently seen in cases of appendicitis.

When one considers the reference of pain from the large bowel, two rather characteristic points may be emphasized. For the most part, colonic pain is typically felt in the hypogastrium, at a level distinctly below a line drawn through the iliac crests. This is the classic pain of colitis, and it is rare for patients duffering from colonic disease not to complain of low abdominal pain which tends to be most severe in the midline. Even localized lesions in the ascending, transverse and descending colon cause a similar reference of painful sensations. There is a striking difference, however, in the localization of pain referred from the fixed points in the colon. Clinical and experimental observations are in agreement that in most instances painful sensations arising from disturbances at the hepatic or the splenic flexure or in the fixed portion of the sigmoid colon are localized over an area closing approximating the site of the pathologic process. Pain at the liver or the splenic flexure is referred typically to the right and left upper quadrants, respectively; and lesions in the sigmoid, as a rule, are definitely associated with pain localized directly over that portion of the large bowel.

Characteristically, the reference of pain from the rectosigmoid is at the midline, localized directly in the suprapubic area or in the midline in the back, over the sacrum. Pain arising from the rectum, again, may be suprapubic or sacral, and occasionally, when the lesion is low in the ampulla, is perineal. Disturbances at any level of the colon may result in a zonal distribution of the pain along a given segment or in pain largely confined to the back at the lower part of the lumbar and the sacral level.

In the light of the preceding observations, it becomes pertinent to emphasize certain other diagnostic aspects of pain referred from the digestive tract. Attention has already been called to the wide variations in individual perception of painful stimuli. Comment has also been made on the fact that pain arising from the duodenum, jejunum and ileum is usually of a sharper nature and more definitely localized than that due to colonic disturbances. Upper esophageal pain is rarely sharp under clinical or experimental conditions, but is usually interprested as a sensation of pressure or fulness. Of still greater clinical interest is the conslusion, derived from distention experiments on normal subjects, that irritation of the lower part of the esophagus frequently results in a sensation indistinguishable from "heartburn." Acute muscular distention of the cardiac end of the esophagus by acid, alkaline, neutral and chemically inert solutions all produced a distinct burning sensation under the lower portion of the sternum. Such a fact is of importance in providing a logical explanation of such a common symptom as pyorisis, or heartburn. As the symptom may occur in the presence of achlorhydria, it is obvious that the chemical nature of the gastric juice cannot constitute the cause of the symptom. The concept that this burning sensation is a variant of referred pain and is due to a localized neuromuscular disturbance in the lower part of the esophagus would seem logical and in keeping with clinical facts.

The occurrence of back pain in relation to gastrointestinal disturbances should be stressed. That such a reference of pain may accompany the anterior pain arising from digestive disturbances is a matter of fairly common knowledge. That pain in the back may be the sole manifestation of such disorders has received little emphasis. Although of relatively uncommon occurrence, it is an important clinical fact that pain at any level of the back may be due entirely to localized disease of the digestive tract. A sudden gastric hemorrhage may provide the first intimation that pain in the tenth dorsal region has been due to a duodenal ulcer rather than to some orthopedic or spinal cord disease. Low lumbosacral pain may disappear immediately on evacuation of the bowels, and the "arthritis of intestinal origin" may be no more than backache due to a rectosigmoid mechanically distended with feces.

It is also important to emphasize again the striking difference in the localization of pain referred from the jejunum and ileum as compared with that due to colonic disease. The relative infrequency of organic lesions limited to the small bowel renders the physician insensitive to this point. Yet, frequently enough the patient's abdominal pain is in reality umbilical pain and is due to one of the less common diseases of the small intestine. In a certain number of instances, involvement of the jejunum or ileum constitutes a complication of already existing disease. Under such circumstances, there is a shift in location of a abdominal pain which is of extreme diagnostic importance. Thus, after a gastroenterostomy or similar operative procedure, the epigastric pain of a typical duodenal ulcer may be replaced by pain in the umbilical area due to the development of a jejunal ulcer. This, in turn, may be replaced by a sensation of discomfort or pain in the hypogastrium due to the development of a jejunocolic fistula. Similarly, the low abdominal discomfort associated with known malignant disease in the pelvis may be altered to definite umbilical pain, peristaltic in nature, owing to a partial obstruction of the ileum, which has become involved in the original pelvic process. A recognition of the importance of a shift in location of abdominal pain is, therefore, of real value in the diagnosis of a new intra-abdominal disease or of a complication of an already existing one.

Another diagnostic feature of digestive tract pain, well recognized but worthy of mention, is the nature of the pain in relation to other physical factors. One should note whether a pain is peristaltic, as well as its relation to the time of day, the position of the patient, the intake of food, bowel activity and the like. One must also differentiate between the steady pain associated with peritoneal irritation and that arising directly from irritation of the digestive tube itself. Furthermore, it must constantly be borne in mind that pain due to a disturbance of the gastrointestinal tract may be entirely dependent on over-stimulation of that portion of the autonomic nervous system supplying a given segment of the tract. So-called functional disease can be responsible for as severe pain of the alimentary tract as that encountered in the presence of organic disease. The pain associated with "mucous colitis," irritable colon, cardiospasm and similar conditions has been the cause of numerous ill-considered operations, because of a failure to appreciate this fact. As the mechanism of pain is identical in patients with organic disease and in those with a local "spasm" due to parasympathetic or sympathetic over-stimulation, it is of fundamental importance to obtain an understanding of the patient in question, as well as of his "disease," before attempting to interpret and treat his symptoms.

Finally, it may be understood that the foregoing presentation of the reference of pain from various levels of the digestive tract, like all other observations obtained on human beings, is subject to exceptions. Variations from the normal expectancy occur, and the diagnosis of alimentary tract disease is frequently far from sure. Such exceptions, however, are not the rule, and a clear understanding of the usual and unusual localization of pain arising from different levels of the gastrointestinal tract will greatly enhance the possibilities of correctly determining the site of its diseases.

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CHAPTER IV

RELATION OF THE TEETH TO GASTROINTESTINAL DISEASES

MASTICATION

Possession of sound teeth, well arranged, has so frequently been associated with good health, not only of the whole body but of the gastrointestinal tract in particular, that the combination of the two is assumed not to be a fortuitous accident but truly to have the relation of cause and effect. Diseased teeth so arranged as to interfere seriously with their primary function do damage in two ways: 1. Food is not adequately comminuted for suitable access by the digestive fluids, and digestion is thereby materially retarded. 2. Diseased teeth and diseased oral mucosa harbor infection and serve to distribute the results of infection to other parts of the body. Furthermore, each of these two factors tends to magnify the effects of the other, so that the progression from bad to worse is in an increasing curve rather than in direct progression.

Since mastication serves not only to reduce the size of food particles but to mix them thoroughly with saliva to facilitate swallowing and bring about the beginning of starch digestion, different foods do not require the same amount of mastication. Study of the masticating apparatus of two types of animals will be sufficient to illustrate this point. The teeth of carnivora are used merely to remove flesh from the carcasses of their prey and to divide it into pieces small enough for swallowing. There is no starch to be digested, and the pieces of flesh need but little preparation for swallowing and no further mechanical modification for effective protein digestion. On the other hand, the food of the herbivora, grain, grass and hay, has to be finely divided and thoroughly mixed with saliva to secure anything comparable to satisfactory digestion. Human teeth have some of the essential structures of both carnivora and herbivors and function, therefore, efficienctly for either the meat or the vegetable type of food.

This compromise is brought about largely by the shorter molar and bicuspid cusps of the human teeth in comparison with those of the carnivora and a greater cups height combined with a smaller grinding area in comparison with the teeth of the herbivora. As a matter of fact, in many of the herbivora, owing to the ingenious arrangement of the enamel, cementum and dentine, there are no true cusps. The human teeth are arranged in the two dental arches so that they do not meet squarely end to end, but each upper molar and bicuspid strikes its antagonist about half a tooth's dimension to the cheek side and the same distance toward the lips. With the mouth in a closed position this causes each of the upper molar and bicuspid cusps to rest in a sulcus or depression in the corresponding lower tooth or between the teeth.

The jaw movements of the human being are more complicated than those of either of the two groups aforementioned. The carnivora have only a chopping motion, as their temporomandibular joint permits only the hinge type of movement. In the cow two movements are found: in addition to the opening and closing movement, there is a wide swing of the mandible laterally, almost in the form of a circle when combined with the first component, so that the contact of the grinding teeth with each other is in the form of a short arc of the whole circle, completed during each cycle of the chewing act. This makes an effective masticating machine, especially because of the absence of marked cusps on the grinding surfaces. In most of the herbivora such a machine is combined with a great capacity of the intestines and stomach, making it possible for them to extract nutriment from a type of food in which the essential constituents are associated in relatively small amounts with a large excess of waste. In addition to the two movements already described, the human mandible has a third one, front to back, usually referred to as protrusion or retrusion, depending on the direction of movement.

For effective mastication it is necessary not only that the teeth be healthy and arranged in the orderly fashion indicated previously, but that there be suitable coöperation of the tongue, lips, cheeks and muscles of mastication. It is equally important that saliva be supplied in the right amount and consistency. Finally, efficiency, as in any other form of muscular activity, is developed by exercise. The necessary factors, therefore, for adequate mastication are intact teeth, their proper arrangement and regular exercise, the last the result of the combination of proper selection of food and good habits of mastication. One method of measuring the functional capacity of the masticating system is to take the strength of the bite by closing the teeth in a given region against a calibrated spring. Usually the first molar region is chosen for this test. High bite registrations determined in this way are found without respect to the size and general muscular development of the subject. Many football players, for example, have relatively low bite measurements. Certain jaw features are characteristic of strong bite, namely, wide dental arches and well developed cheek and temporal muscles. Any form of systematic exercise, except when the teeth are seriously diseased or badly formed or arranged, will greatly increase the bite force, provided it is not already at a high level; the exercise may be supplied by chewing refractory foods or indeed even by chewing paraffin or gum vigorously for from ten to twenty minutes three times daily. Like other forms of muscular development, maximum efficiency is maintained only by continuous and regular use within physiologic limits.

Just to what degree, if any, lack of mastication of food has to do with diseases of the digestive tract and indigestion is questionable. Certainly the size of the protein fragments, at least within the size that can be conveniently swallowed, has little influence on their digestion. It is true that chewing and the saliva secreted as the result of the activation of the salivary glands by chewing are definite aids in stimulating gastric secretion and gastric activity. On the other hand, the ability of the digestive system to extract the valuable constituents of the fresh fruits and vegetables, especially the necessary minerals, vitamins and activators, is without doubt highly dependent on the degree of the comminution of food during mastication. Since these are just the food substances that tend to deteriorate or are destroyed as the result of heating, storage and refining, it is perhaps most important that the mastication of uncooked vegetables and fruits, especially the former, be as thorough as is practicable. If this function is measurably deficient, consideration should be given to it with respect to the forms of disease that have to do with deficient mineralization and avitaminosis.

The digestion and metabolism of edentulous persons either with or without the assistance of artificial dentures is probably worthy of more extensive study than has apparently ever been given to it. Certainly such persons learn to get along surprisingly well, in spite of the fact that the very best sets of artificial dentures measured by the bite force test give results that are never more than 25 per cent of those obtained for natural teeth in only a fair state of functional capacity. Some of these artificial dentures that rate rather low by the bite foce test, however, seem to give their owners as much satisfaction as those with a higher bite force rating. Here it seems to be a matter of the skill and good judgment with which the owner uses his less efficient dentures.

In connection with mastication, mention should be made of a subject belonging to a later section. Persons with advanced pyorrhea have natural dentures that are indeed much less effective as chewing machines than even poor artificial ones. It is a rather striking and regular occurrence that the relief of advanced pyorrhea either by extraction of the teeth or by a combination of extraction and some other form of treatment and associated with the replacement of missing teeth by suitable substitutes is almost always followed by a great improvement in the patients' general condition. They gain weight; they have a greater degree of vitality; they resist fatigue better and feel better. Whether this gain is due to the elimination of infection or is the result of the improvement of mastication is not wholly certain. However much the inclination to ascribe the improvement all to the elimination of a focus of infection, the purely mechanical situation should not be overlooked. Some share of the improvement is without doubt in many instances caused by the better digestion and better assimilation of food.

TEETH AS FOCI OF INFECTION

Diseased teeth, since the first step in the process is dental decay, not only interfere with mastication but contribute directly to chronic types of disease elsewhere in the body, including the gastrointestinal system. This is by no means an exclusive property of infected teeth and is in no essential matter different from the action of primary foci of infection elsewhere in the body, such as the tonsils. There are two distinct methods by which the damage is done. 1. Bacteria, chiefly streptococci and staphylococci, become established within the tissues at the apex of a tooth or in the walls of a pyorrhea pocket. Under favorable circumstances at some later time these same organisms find entrance into the circulation from this primary focus and colonize in one or more remote parts of the body, establishing a secondary focus of infection. 2. The bacteria remain localized in the primary focus and do not metastasize, but some sort of toxic material, some waste product of bacterial metabolism within the tissues of the primary focus or some from of bacterial protein, is carried by the body fluids to distant parts of the body, causing some sort of toxemia as a secondary process. Clinically, the second type may be dealt with the more satisfactorily, since removal of the primary focus is promptly followed by relief of the secondary symptoms and resolution of the secondary lesion. There are four specific forms of the primary focus in the dental apparatus, namely, periapical granuloma, vital pulp infection, infection of partly erupted teeth and pyorrhea. Pyorrhea is used throughout this section to designate the chronic condition of the gums due to inflammation, rather than the more exact terms, such as periodontitis, used by dentists specializing in its treatment.

Periapical Type of Primary Focus.—This is a frequent result of the exposure of the pulp by dental caries and the subsequent invasion of the pulp and periapical space by streptococci and staphylococci from the oral cavity. The specific invading organisms are usually *Streptococcus viridans* and the oral staphylococcus strain; however, other bacteria may associate themselves with these in the primary focus but have little or nothing to do with the secondary forms. The degree of irritation caused by invasion of the apical region by these bacteria is not great enough to cause much, if any, necrosis, and pus or exudate formation is rare. Since the reaction is chiefly proliferative, the effect of the increasing amount of chronic granulation tissue causes resorption of the adjacent alveolar bone, so that the loss of bone around the apex will be recorded on a roentgenogram. There are at least three types of periapical reaction, namely, fibrous, infiltrative and cystic, all three of which are definitely associated with demonstrable bone resorption but only one of which can be seriously considered as a primary focus of infection. The fibrous form is the result of a mild grade of infectious irritation in either a late or an early stage. In it all the reactions that are associated with the presence of bacteria in the tissues are absent. It can be assumed that the reaction is only toxic or mechanical. The cystic type is a late phase of the conversion of either of the other two into a dental root cyst. In this form the epithelium from which the lining of the cyst develops originates from the epithelial remnants of the enamel organ from which the tooth originally developed. Only in case these have not completely atrophied or there has been a connection through a discharging sinus lined with the mouth epithelium do dental root cysts develop, as there seem to be only the two possible sources of the epithelium necessary for the formation of the cyst lining. Since the contents of the cyst are generally sterile, the dental root cyst and the cystic granuloma cannot be considered as primary foci of infection. Infection of these cysts usually results in the formation of an abscess, which either ruptures and discharges or has to be drained surgically.

The infiltrative form is made up of richly vascular granulation tissue; usually the more central portion has all the earmarks of the type of infiltration associated with the presence of bacteria, such as polymorphonuclear and plasma cell accumulations. There is no question about its being a possibly primary focus of infection. It is also the type of infection which is found associated with pulpless teeth (so-called dead or nonvital teeth). Concerning these teeth there are so much controversy and such sharply divided schools of thought that but little will be said about them, except to emphasize the point that teeth, from the point of view of this argument, should be considered simply as either infected or not infected. If the tooth is infected it makes but little difference whether it is vital, dead or pulpless. If it is not infected, that is the important consideration. In a later paragraph infections of vital teeth will be discussed as primary foci. There is one undisputed fact about pulpless teeth: They are very prone to infection,

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and periapical infections of pulpless teeth exceed greatly all other forms of periapical infection. The periapical space at the root of a pulpless tooth is presumably much less resistant than that of a healthy tooth to bacterial invasion either by direct extension or by invasion from some distant part of the body by way of the blood. The single-rooted anterior teeth have a somewhat better record than the multirooted posterior teeth, perhaps because they offer easier access for root canal treatment. It should be pointed out that extraction of a pulpless tooth can only benefit a patient's condition if by its removal the primary infection is eliminated. If infection is not present in the extracted tooth there will be no permanent change in the form of continued improvement. The roentgenogram is of great assistance in the selection of infected teeth; however, it is merely a shadow picture, and its interpretation cannot be final. What appears to be a region of resorption in the film may prove to be the shadow of a cyst, or a region of resorption may be hidden by the tooth or a thick layer of dense bone, either of which may wholly nullify the evidence of a small region of resorption.

Vital Pulp Infection.—It is the custom of dentists now to avoid as far as possible the exposure of a pulp in the preparation of cavities for fillings and to do as few root canal fillings as possible. As a result of this, the number of large restorations, especially inlays and amalgam fillings, is gradually increasing. More crowns are placed over vital pulps. Many of these cavity preparations are carried close to the tooth pulp. There is no question but that the number of both acute and chronic pulp infections under large restorations is increasing. The chronic forms are typical primary foci of infection. As a rule, the secondary manifestations are largely sensory and toxic, and the gastrointestinal tract is generally spared. Some of the secondary complaints are headache, neuralgia-like pains, often referred to some remote part of the head or neck region, loss of appetite and insomnia. Only one feature of this form of infection deserves emphasis, namely, that because of the bias and prejudice with respect to the pulpless tooth this form of primary oral focal infection is frequently overlooked.

Infection of Partly Erupted Teeth.—Although impacted or unerupted teeth that are wholly within the bone or soft tissue are only rarely primary foci of infection and then only after they have become the site of a definite infectious process, partly erupted teeth, especially third molars, are to be viewed with great suspicion. Since the condition about the exposed crowns is generally similar to that of pyorrhea, no discussion beyond that found in the section on that subject is necessary.

Significance of Oral Focal Infection.—On the whole, the etiologic significance of chronic forms of oral infection is given insufficient consideration in diagnostic and therapeutic programs involving other parts of the body. Yet evidence accumulating shows that the mouth is an effective portal of entry for bacteria into either the blood stream or lymph channels. For this reason, teeth with definitely infected pulp or periapical regions and teeth with advanced pyorrhea and so loose as to move easily in their sockets must not be tolerated. Moreover, extraction of teeth associated with deep pyorrhea pockets or the infiltrative type of periapical infection must be by methods which will definitely hinder or wholly inhibit the forcing of bacteria into bloodvessels or lymph channels.

Pyorrhea and Related Conditions.—There are three types of damage done by pyorrhea, a prevalent disease of the oral tissues. The discharge of septic material from the pus pockets may be considerable. As this material is swallowed it is possible that the contained bacteria at times escape the destructive action of the gastric juice and that the purulent material may be absorbed before it is ultimately digested. However, it seems probable that most of the bacteria are killed and that practically all the toxic substances in the pus are destroyed by digestion either in the stomach or in the small bowel. It is certain that the same toxic materials are absorbed through the thin walls of the pocket side in the gums. The covering of epithelical cells over the capillary loops of the inflamed pocket lining is in places not more than two or three cell layers in thickness, without keratinization and always wet; diffusion of substances already in solution through such a membrane is therefore easy. The loss of weight, lack of appetite and absence of a sense of well-being all may be caused by absorption through the pockey lining just as well as by swallowing of the discharge, and somewhat more plausibly so. In reality it makes but little difference which of the explanations is the more acceptable; the end-result is the same in either case.

As the pyorrhea pockets deepen, the teeth become so loose in their sockets that considerable movement can be produced with the application of relatively little force. Rocking these in their sockets either during mastication or even during their extraction tends to compress the material within the socket. If there is any interference with drainage, as by a ledge of calculus or any other obstruction, bacteria and other material from the pus and exudate will be forced into the superficial layers of the deeper parts of the pocket lining. Under such circumstances it may be inferred that bacteria and other substances are literally pumped into the tissue fluids and thereby find their way into the circulation. It is not strange that mouth bacteria can be demonstrated in the blood shortly after such manipulation or after forceps extraction of the teeth in a high percentage of the cases studied. Especially is this true if the pockets are deep and the pumping action in the effort to deliver the tooth is marked, for in spite of their looseness such teeth are removed with considerable difficulty. It would seem that the loose tooth affected by pyorrhea is an effective agent favoring the dissemination of mouth bacteria to other parts of the body from the standpoint of focal infection. Only the low virulence of the organisms prevents the establishment of numerous secondary foci. This point of view is in harmony with the fact that elimination of the pyorrhea is generally followed by a definite improvement in the patient's general health, including increase in weight, improved appetite and better digestion.

The association of pyorrhea with other diseases and disease conditions should be kept in mind. Uncontrolled diabetes is regularly complicated by a malignant form of this type of gingival disease. Nearly all the victims of definite constipation suffer from some sort of gum disturbance, sometimes in the form of obstinate and chronic pyorrhea. Correction of the bowel condition is of marked value in the therapy of the gum condition. Both A and B avitamoses act unfavorably on the gums and oral mucosa, tending to exaggerate the symptoms of both gingivitis and pyorrhea. Of course if the deficiencies are marked, especially that of vitamin C, the reaction is in the form of a specific stomatitis. Although not wholly pertinent to the subject at this point, it should be noted that a type of gingivitis that partly resembles the Vincent form and also is somewhat suggestive of the acute exacerbations of pyorrhea ushers in a considerable number of diseases of the blood-forming organs, such as the leukemias, agranulocytic angina and pernicious anemia.

Mercurial stomatitis frequently follows the use of mercurial preparations therapeutically. For the most part it is wholly preventable, as it occurs chiefly in the mouths of subjects whose teeth are diseased and have had little or no attention of any kind. Before mercurial treatment is instituted care should be taken to eliminate all infection, including pyorrhea pockets, calculus and any other pathologic conditions that may be found. Treatment of the established stomatitis begins with withdrawal of the drug. As soon as the acute symptoms have subsided, a beginning should be made as just outlined and the preparation completed before administrtion of the drugs is resumed.

Most of the effects and symptoms of pyorrhea disappear with the extraction of the tooth involved in the process. On the other hand, the sacrifice of the tooth can be prevented or at least delayed by eradication of the pus pocket and the elimination of the conditions which caused the lesions. Many of the etiologic factors are chiefly local and can be eliminated by intelligent and skilful treatment of the dental situation. When the systemic factors are of afelatively much greater magnitude than those of local origin, their correction outweighs local treatment.

DISTURBANCES OF TASTE AND SENSATION

The frequency and variety of complaints that have to do with change in sensation and taste are numerous. At the same time there is no condition of the oral cavity for which the explanations from the standpoint both of the clinician and of the patient are less satisfactory. One considerable fraction of these disorders includes all those associated with lesions and disease of the central nervous system or the peripheral sensory nerves. Loss of taste or taste disturbances may be referred to disease of the chorda tympani nerve. Another fraction includes the abnormalities of taste which are symptomatic of metallic poisoning or intoxication, such as a peculiar metallic taste in mercurialism, the sweetish taste that goes with plumbism and the metallic sensation associated with arsenical poisoning.

The supposition that the use of dissimilar metals in the mouth in the form of restorations causes taste peculizrities as well as erosions, ulcers, leukoplakia and other forms of local irritations is not wholly new. The subjective sensations listed as being caused by this condition are salty or metallic taste, burning or stinging of the tongue and cheek and even dryness or tickling of the throat. These conditions are supposed to arise in the soft tissues where *dissimilar metals make intermittent contacts*. Although the existence of such pathologic conditions cannot be denied categorically, the frequency of their occurrence cannot be as great as the proponents of the hypothesis assume. Bias in favor of it should not be carried to the extent that the elimination of other factors which can cause the same conditions is overlooked. Certainly in a definite case of this kind the lesions will be relieved promptly by correction of the situation. Even grinding off of one filling so that its contact with another of a different metal is eliminated should be sufficient. At least there is no reason for the condemnation of all the fillings of dissimilar metals and for the replacement of some with others so as to make them all alike with respect to electrical properties. Electrical potentials are developed between different types of gold, especially since all types of dental gold are not pure metal but alloys. Even specimens of gold of the same chemical formula may become different electrically through differences in heating, tempering and casting.

Burning sensations of the tongue and cheeks, especially in women at or just beyond the menopause, are not uncommon. Frequently these subjective sensations are associated with an intense fear that they indicate the onset of cancer. As a matter of fact, they are rarely, if ever, found in mouth cancer, the early stages of which are notoriously symptomless, except for the formation of a swelling or painless ulceration, often on the foundation of preëxisting leukoplakia. One clue for their management and treatment is found in the age and sex of the patient. There is no definite proof other than that of clinical experience that there is a relation to the menopause, but the assumption is useful because some form of treatment based on the suspected menopausal origin may be instituted.

Rubber sore mouth is partly similar to the two foregoing conditions, although it has a somewhat more substantial foundation as a clinical entity. It has been ascribed to impurities in the rubber used in the offending denture, such as the vermilion content; to careless vulcanization of the rubber, causing irregularities or increased porosity; to the insulating characteristics of the material, and to failure to keep the dentures clean. To these possible etiologic factors should be added the possibility of a lack of mechanical perfection in the adaptation of the dentures to the soft tissues. The subjective sensations are chiefly those of mechanical or inflammatory irritation. Correction of the dentures based on the facts disclosed by a careful examination and on the etiologic possibilities will usually convert an unsatisfactory restoration to one that is sufficiently effective for all necessary purposes and causes no undue irritation. It is always somewhat difficult for the patient to adapt himself to artificial dentures, and the older he is at the time the adjustment has to be made, the greater the struggle.

DENTAL CARIES AND RELATED SUBJECTS

Dental caries is primarily a disease of the earlier decades of life, a disease which without any assistance from other etiologic agents is capable of bringing about wholly inadequate mastication and causing the periapical type of primary focus of infection. It is almost universal, and its incidence seems to be on the increase, even in spite of the preventive activities of the past two or three decades. Somewhere between 80 and 90 per cent of the teeth lost are doomed by either dental decay or pyorrhea; the division between the two is about equal. Pyorrhea operates in the last decades of life and is distinctly related to involution and senility. On the other hand, caries is most prevalent and most destructive in the first two decades. Since a persons suffers most and is crippled irreparably when his masticating capacities are handicapped during his growing years, the ultimate damage done by caries is greatly in excess of that caused by pyorrhea.

Caries of the teeth is both a fluctuating and an intermittent process.

The fluctuations are at least seasonal and epochal; the periods covered by this type of fluctuation—and this includes both the period of activity and that of remission—are long ones. During the period of activity the actual moments of tooth destruction, according to recent investigations, are relatively short and highly intermittent. Only when all the necessary conditions are wholly favorable is acid formed and tooth substance destroyed. These necessary favorable circumstances are, at the least, a source of a fermentable carbohydrate, bacteria capable of forming acid from the sugars and starches and finally a sheltered environment in close approximation to the surface of the tooth. The menace of sugars and other carbohydrates in general is in direct proportion to their solubility and the concentration of the solution. Either the lodging of a starch particle against a tooth surface relatively inaccessible to saliva in a deep groove or pit or the transitory apposition of concentrated sugar, as from candy, to even a broad surface on either the buccal or lingual surface of a tooth may be effective.

The well known attempt to break up this combination by destroying the bacteria with germicides, dentifrices and toothbrushes is, relatively speaking, a failure. The reason for this failure in the light of present knowledge is not difficult of comprehension. It has served to sharpen interest in a much more promising procedure, namely, the limitation of sugar and starch (especially sugar) consumption to a degree at which acid is not produced at the points where decay occurs. This plan has worked rather consistently both forward and backward. Decrease in the ingestion of sugars and starches has been associated with corresponding decrease in the activity of the carious process. On the other hand, increase in ingestion of the same type of food has been accompanied by proportional increase in the activity of tooth destruction. However, this is only relatively true, as there seems to be a small group of persons in whom a high degree of immunity to the process and of resistance to the effect of the ingestion of fermentable carbohydrates exist. On the opposite side is another small group of highly susceptible persons whose sugar and starch reduction (with special emphasis on sugar) to be successful has to be carried close to complete abstinence.

To facilitate the management of individual cases by this plan clinicians must have some form of laboratory test analogous to the laboratory tests for sugar in blood and urine used in the control of diabetes—in other words, a reliable, relatively simple test for contemporary caries activity. As caries is both fluctuating and intermittent, no adequate information of this kind can be obtained by clinical or roentgen examination. The clinician and patient must know whether the decay is active or dormant in order to achieve anything comparable to progressive control of the situation. Two such tests are now available, one chemical and the other bacteriologic. Use of either one makes it possible for the physician or dentist to control activity by manipulation of the diet of the patient so as to hold the proportion of sugars and starches within that tolerated by the patient where dental caries is concerned. Certainly enough now is known about dental decay to warrant measures calculated to effect material reduction in its occurrence, chiefly reduction of the amount of the highly soluble and highly concentrated sugars. This is essential only when the process is highly active and while the person is shown to be susceptible by the laboratory tests described herein. Although something is known about the inhibition of decay with fluorides and other chemical substances, it is not yet practical to use these agents for either individuals or large groups.

As far as caries and pyorrhea are concerned, teeth are definitely sensitive to the environment in which they exist, and in this sense they should be somewhat of an index of body health and vigor. As long as they function adequately for the efficient mastication of food, are used wisely for that purpose and are spared from infection and decay, they contribute their share to the welfare of the whole body, including the gastrointestinal tract. Under these conditions they are never a hazard or menace to the body. But once they have become involved by pathologic processes they supply a real problem to both physicians and dentists.

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PART II

The Esophagus, Stomach and Duodenum

CHAPTER V

DISEASES OF THE ESOPHAGUS

No portion of the alimentary tract is subject to a greater variety of diseases than the esophagus, and although esophageal lesions are not rare, they frequently are overlooked because of a lack of appreciation of the significance of dysphagia. Too often, dysphagia is confused with globus hystericus, and inability to swallow food is attributed to nervousness.

Whenever a patient experiences difficulty in swallowing, complete physical examination in addition to exhaustive investigation of the esophagus is indicated. In more than 90 per cent of patients suffering from dysphagia complete investigation will reveal a lesion in the esophagus. A "lump in the throat," peculiar sensations in the region of the esophagus and similar indefinite symptoms are seldom indicative of disease, but rather are somatic manifestations of an unstable nervous system. Unfortunately, development of the esophagoscope has had a tendency to magnify the importance of direct inspection and to minimize the value of considering the esophageal findings as a part of a general diagnostic problem.

Every patient who suffers from symptoms referable to the esophagus should have the same careful recording of history and physical examination as that accorded a patient with an obscure digestive disturbance. Particular attention should be given to the history of onset of symptoms and progress of discomfort. Sudden onset of dysphagia during the eating of a pork chop or creamed chicken should suggest the possibility of a foreign body's having become impacted in the esophagus, especially if the patient has dental plates which may interfere with detection of a solid substance in the mouth during mastication.

The patient's age, possible ingection of a caustic solution, history of malignant disease in the family, association of other digestive disorders and the progressive or intermittent occurrence of symptoms are important factors in determining the type of lesion responsible. A history, carefully elicited, is of paramount importance in diaanosis and management.

Physical examination usually discloses loss of weight if ingestion of food has been hindered. Metastatic lymphatic nodes may be found in the cervical or axillary areas, or an epigastric mass may be palpable if esophageal obstruction has resulted from carcinoma. Anemia may be present with carcinoma of the esophagus if bleeding has occurred and is frequently noted with hysterical dysphagia or Plummer-Vinson syndrome. Enlargement of the spleen in association with secondary anemia is also observed with hysterical dysphagia. Bilateral pulmonary infection or unilateral acute pulmonary abscess may result from aspiration of food or secretion from the esophagus into the respiratory tract.

Laboratory studies should include complete investigation of the blood and urine. Roentgen study of the thorax should be made to determine the presence or absence of a foreign body in the esophagus or of a tumor in the mediastinum. A mixture of barium can be administered by mouth for detection of the location and type of esophageal obstruction, provided dysphagia is not severe and the presence of a foreign body is not suspected. When dysphagia is so severe that the patient has difficulty in swallowing liquid, administration of barium by mouth may cause complete esophageal occlusion, and gastrostomy may be required to introduce fluid into the stomach. In the presence of a foreign body, ingestion of barium may cover the object and increase the difficulty and risk of removal at the time of esophagoscopy.

Esophagoscopy is imperative in the removal of a foreign body from the esophagus and permits visualization and removal of tissue from a lesion involving the esophagus. Esophagoscopy is not required by all patients who have dysphagia and should be deferred until after other studies.

CARCINOMA OF THE ESOPHAGUS

From 5 to 7 per cent of all carcinoma in men occurs in the esophagus, and reduction in the lumen of the esophagus from a malignant growth is the most common cause of difficulty in swallowing. Carcinoma of the esophagus is five or six times more frequent in men than in women and is seldom encountered in patients under forty. Although any portion of the esophagus may be involved with malignant growth, the chief points at which carcinoma is encountered are the pharyngoesophageal junction, the middle portion of the esophagus (11 to 14 inches from the incisor teeth) and the junction of the esophagus and stomach. In men at least half of the malignant growths in the esophagus are located at the cardia, whereas in women more than half have their origin in the hypopharyngeal region.

The earliest symptom of esophageal carcinoma is obstruction to the passage of solid food at the location of the growth. If dysphagia is first noted when the patient is eating rapidly, care in mastication may prevent symptoms for several weeks. As the lumen of the esophagus is reduced in size, however, from enlargement of the growth, dysphagia becomes progressive until finally there is marked difficulty in swallowing liquid. The duration of symptoms from the onset of complete esophageal obstruction is about seven months. Regurgitation of food is a rare symptom until obstruction to liquid becomes complete. Prior to this time the patient is careful to eat only those foods which pass the area of narrowing in the esophagus. Pain is seldom experienced until the growth has extended beyond the wall of the esophagus. Bleeding may occur during the course of the disease but is not an early symptom. Hemorrhage is frequently the cause of death. Hiccough is often noted, especially when the growth is located at the cardia.

As the intake of food becomes restricted, the patient loses weight and strength, and an appearance of cachexia develops before anemia can be demonstrated by laboratory study. Concentration of hemoglobin and cellular elements due to dehydration may explain the normal blood picture. Although metastasis occurs in neighboring lymphatic nodes relatively early in the disease, spread of the growth to superficial nodes is usually a late manifestation. Ulceration of a carcinomatous growth from the esophagus into the trachea or a bronchus may occur with formation of a fistula (Fig. 28). When fistula has developed, the swallowing of liquid is followed by strangulation and severe attacks of cough.

Roentgen study after ingestion of barium usually reveals an obstruction with irregular outline. When fistula has developed, the opening into the air passages is usually demonstrable by leakage of the radio-opaque barium into the trachea or a bronchus. Carcinoma in the hypopharyngeal region may cause an overflow of barium into the trachea if the patient swallows the mixture too rapidly, and an erroneous diagnosis of esophagotracheal fistula may result.

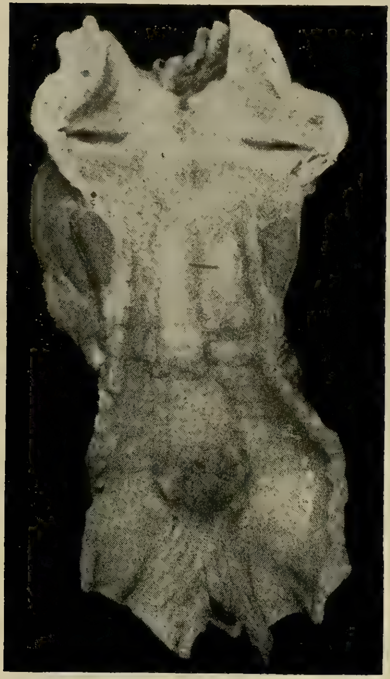

Fig. 28.—Ulceration of carcinoma of the esophagus into the trachea, with formation of an esophagotracheal fistula.

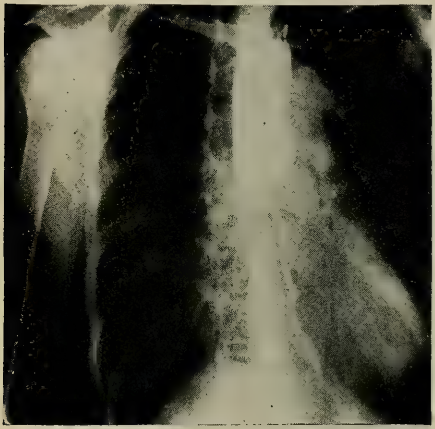

Fig. 29.—Carcinoma of the esophagus. The patient was relieved from dysphagia for a year after dilation of the stricture.

Esophagoscopy is indicated whenever doubt exists as to the exact nature of a lesion obstructing the esophagus, for in a considerable number of cases a benign lesion may appear malignant if roentgenoscopy only is employed in diagnosis.

Treatment.—Treatment of carcinoma of the esophagus is unsatisfactory, and almsot all patients who have the disease succumb within fourteen months after the onset of symptoms. Successful resection of the esophagus for carcinoma has been accomplished on several occasions, but most of the patients have died of shock soon after operation or later from a local or general recurrence. Radical removal of malignant esophageal growths is still in the experimental stage. Treatment with radium and high voltage roentgen rays has possibly retarded progress of the growth in a few instances, but the ultimate results have been unsatisfactory.

Gastrostomy has been advocated as a palliative procedure, but patients frequently are made more uncomfortable by the operation. As gastrostomy carries a mortality rate of 10 to 50 per cent, it cannot be recommended enthusiastically. Intubation of growths in the esophagus may prove helpful in prolonging life and increasing comfort, but blocking of the tube by the growth or food may interfere with feeding.

Dilation of the carcinomatous esophagus by metal sounds passed into the stomach over a previously swallowed, twisted silk thread usually provides more comfort for the patient than any other type of treatment (Fig. 29). Risk in stretching the stricture is negligible; and when large sounds (45 French) are passed through the area of stenosis, freedom from dysphagia is usually obtained for six or eight weeks and frequently for longer periods. Further dilation may be employed when closure recurs, and life with comfort may be prolonged indefinitely.

CICATRICIAL STRICTURE OF THE ESOPHAGUS

Healing of an inflammatory lesion in the esophagus may result in reduction of the lumen of the tube and interference with passage of food into the stomach (Fig. 30). The degree of dysphagia usually depends on the extent of the stricture and the size of the lumen through the area of stenosis. However, patients having a short stricture with a wide lumen that can be dilated with ease to a large size may experience more difficulty in swallowing than patients having a much more extensive area of stenosis.

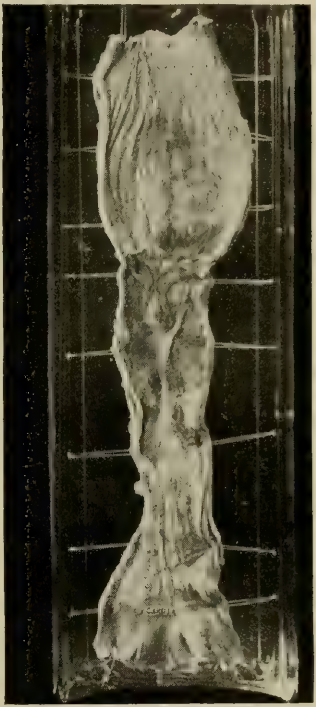

Fig. 30.—Scarring and contraction of the esophagus following ingestion of lye.

Accidental or intentional ingestion of a corrosive substance, such as potassium and sodium hydroxide or a strong inorganic acid, is responsible for many benign strictures in the esophagus. Other causes are typhoid fever, scarlet fever and vomiting with pregnancy. In one-fifth of the cases the cause cannot be determined. When the origin is unknown, carcinoma is frequently suspected. A diagnosis of carcinoma of the esophagus is unwise unless tissue removed from the lesion reveals unmistakable evidence of malignant change when examined by a competent pathologist. Even when this precaution has been observed, I have seen several errors in diagnosis. It is best, therefore, to treat all strictures of the esophagus as benign unless surgical removal of a growth is contemplated.

When a burn of the esophagus has resulted from ingestion of a corrosive substance, there is usually an associated burn of the lips, mouth and hypopharynx. Dysphagia is a prominent symptom at the onset, but as the acute inflammatory reaction subsides, deglutition may improve or become normal. As healing progresses, the lumen of the esophagus contracts, and interference with swallowing is again noted. Within six weeks after ingestion of a caustic substance the caliber of the stricture is reduced so that fluid is swallowed with difficulty, and treatment is required.

With stricture from other causes, difficulty in swallowing is the only symptom. Frequently there is a short area of stenosis with a wide lumen in the esophagus, so that the patient may swallow any type of food as long as it is eaten slowly and masticated thoroughly. Dysphagia may be noted occasionally when corase food is eaten or when deglutition is more rapid than usual.

In cases of benign stricture roentgen examination after ingestion of barium usually reveals smooth obstruction, but when more than one stricture is present, areas of narrowing distal to the first one may not be demonstrable. Particles of food in the esophagus above a stricture may present irregularities which suggest malignant growth. When stricture has followed ingestion of a caustic substance roentgenoscopy is seldom necessary for diagnosis or as an aid in treatment. Esophagoscopic examination should be made in cases of benign stricture when the presence of carcinoma or a foreign body is suspected, but direct inspection of all cicatricial strictures is not desirable.

Treatment.—Treatment for benign stricture consists of gradual dilation of the area of stenosis, which can be accomplished best by passing metal sounds on a whalebone staff over a previously swallowed twisted silk thread. Sounds of increasing size are passed through the lumen of the stricture, and the interval between dilations is gradually extended. At the time of the first dilation it is usually possible to pass a size 30 French sound through the stricture. A week or ten days later a sound two or three sizes larger is introduced into the stomach. After an interval of ten to twenty days, sounds of increasing size are employed until a large sound (45 French) can be passed through the esophagus. Not more than one sound should be introduced through the area of stenosis at each treatment, because too frequent passage of dilators will traumatize the area of inflammation in the esophagus and delay healing.

Gastrostomy is seldom necessary and should not be performed unless death from starvation is imminent. Complete organic stenosis is not often observed, but when it is present the lumen of the esophagus can rarely be restored. Reconstruction of the esophagus by various operative procedures has been accomplished in a few cases.

CONGENITAL STRICTURE OF THE ESOPHAGUS

Congenital malformation of the esophagus is not infrequently encountered in the newly born, and when the deformity is associated with complete obstruction the infant rarely survives for more than a week or ten days.

In the most common variety of congenital malformation the upper end of the esophagus consists of a blind pouch, the distal end communicating with the trachea. Regurgitation of fluid immediately after swallowing, strangulation and abdominal distention are outstanding symptoms. Associated deformity in the gastrointestinal tract, especially imperforate anus, has frequently been reported.

Occasionally the congenital defect consists of a membranous stricture with a small aperture which allows passage of fluid into the stomach (Fig. 31). Many patients obtain sufficient nourishment to permit normal development. This type of stricture is always short and can be dilated with ease to size 45 French. In many instances one divulsion of the stricture is enough to produce complete and permanent relief from dysphagia. In others occasional passage of a sound through the stricture for varying periods is required before permanent relief is obtained. A silk thread is used as a guide for passing sounds, as for other types of stricture.

CARDIOSPASM

One of the most interesting lesions that produces difficulty in swallowing is commonly known as cardiospasm, or idiopathic dilatation of the esophagus without anatomic stenosis. The disease is characterized by dysphagia, regurgitation of food and epigastric pain. Symptoms may begin suddenly or gradually and may vary in intensity, although the difficulty is constant until relieved by appropriate treatment. Men are affected more often than women. Cardiospasm may be observed at any time of life, but is more frequent during the third and fourth decades.

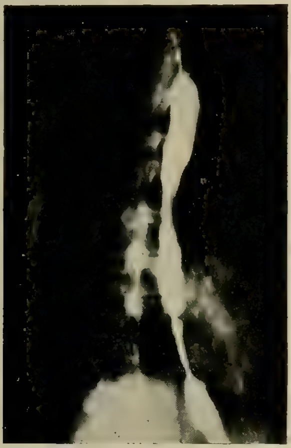

Fig. 31.—Congenital stricture of the esophagus.

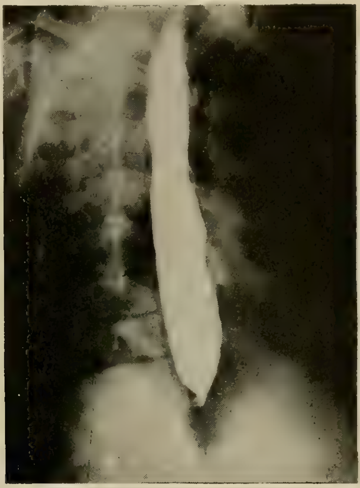

Fig. 32.—Cardiospasm, with moderate dilatation of the esophagus above the area of obstruction.

Difficulty in swallowing both solid and liquid food, especially cold water or carbonated beverages, is a prominent feature. The sense of obstruction is usually noted at the cardia, although it may be located in the neck. Complete obstruction may be experienced for several days at a time, after which deglutition may improve, though it seldom becomes normal without treatment. At the onset, regurgitation may occur immediately after swallowing; later, regurgitation may be delayed and may occur during sleep, resulting in aspiration of material from the esophagus and strangulation. Chronic pulmonary infection or acute pulmonary abscess may follow prolonged regurgitation and aspiration of secretion from the esophagus.

Epigastric pain radiating to the back or substernally to the neck, ears and lower jaw is noted in 60 per cent of patients with cardiospasm. Pain may be the initial symptom and may be of such severity that it is confused with gallstone colic or coronary heart disease. As cardiospasm progresses, pain frequently lessens. Usually it occurs independent of swallowing.

Roentgen examination in cases of cardiospasm reveals smooth obstruction at the cardia with more or less dilatation of the esophagus above the area of stenosis (Fig. 32). At times the esophagus may be dilated so that it will hold a quart or more of food. In a few cases pressure in the mediastinum from the dilated esophagus filled with food has produced considerable respiratory distress. When the esophagus is only moderately dilated, small pieces of food may be retained at the cardia, producing defects in the contour of the tube which may sometimes be mistaken for carcinoma.

Esophagoscopic examination is rarely necessary, but when required, local anesthesia should be employed. Should food be retained in the esophagus, it will frequently be regurgitated during general anesthesia and may be aspirated into the lung, with a fatal result.

Treatment.—Many types of treatment have been employed in the management of cardiospasm, but the most effective is dilation of the cardia with large sounds or an expanding type of dilator. After the patient has swallowed 4 or 5 yards of twisted silk thread, sounds may be passed over the thread through the cardia with only slight resistance. Passage of a size 60 French sound will produce temporary relief from dysphagia in 10 per cent of all patients. In half of this group relief is permanent, whereas the remaining half, like the 90 per cent not relieved by passage of sounds, require dilation with some type of expanding dilator before normal deglutition can be restored. Twenty-five per cent of the patients who have the cardia dilated with an expanding dilator subsequently have a mild recurrence of symptoms that may produce sufficient annoyance to require further dilation, while 75 per cent remain free from dysphagia after treatment. Complete relief from symptoms can be obtained in almost all patients with cardiospasm, provided dilation is repeated in those who have recurrence of dysphagia. If stretching of the cardia with an expanding dilator is reserved for patients who have not obtained relief from dysphagia by passage of a 60 French sound, the risk of treatment is negligible.

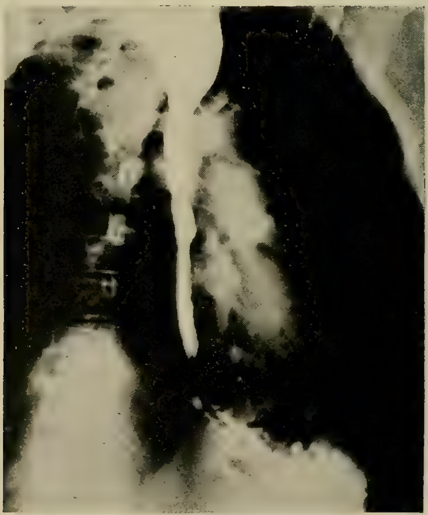

Fig. 33.—Typical roentgenogram of diffuse spasm of the esophagus.

DIFFUSE SPASM OF THE ESOPHAGUS

Diffuse spasm of the esophagus may produce symptoms indistinguishable from those of cardiospasm, but complete esophageal obstruction is noted more often in patients with diffuse spasm than in those who suffer from cardiospasm. Periods of complete freedom from dysphagia may also be noted with diffuse spasm, whereas with cardiospasm difficulty in swallowing is continuously present.

Roentgen study is usually sufficient to differentiate diffuse spasm of the esophagus from cardiospasm (Fig. 33). In diffuse spasm the distal half of the esophagus is spastically contracted, and rarely is there much dilatation of the proximal portion. Diffuse spasm of the esophagus may be associated with an intra-abdominal lesion (frequently disease in the gallbladder), whereas cardiospasm is usually an independent disease.

Intermittent spasm at the cardia often produces mild dysphagia but rarely causes sufficient obstruction to permit detection by roentgen study. Stretching of the cardia may be indicated when symptoms are troublesome, even though definite obstruction cannot be demonstrated by esophagoscopy, or roentgenoscopy.

DIVERTICULA OF THE ESOPHAGUS

Diverticula of the esophagus are of three types: traction, pulsion and tration-pulsion.

Traction diverticulum, the most common type, is usually located in the region of the left main bronchus and often results from an extraesophageal inflammatory lesion which involves the wall of the esophagus. As healing occurs, the wall of the esophagus is pulled outward and upward and a tiny sacculation is formed, which usually does not produce symptoms but is frequently found at postmortem examination. Occasionally this type of diverticulum will rupture into the mediastinum or left bronchus, with formation of an abscess or esophagobronchial fistula.

On rare occasions an obstructive lesion in the esophagus beyond the mouth of the diverticulum will promote accumulation of food in the sac. Increased intraesophageal [8]pressure will produce enlargement of the sac with formation of a traction-pulsion type of diverticulum (Fig. 34).

The type second in frequency and first in clinical importance is the pulsion diverticulum, usually observed at the junction of the hypopharynx and esophagus and really of pharyngeal rather than esophageal origin (Fig. 35). It occurs in men much more often than in women and usually not before the age of forty; the majority of patients with this type of diverticulum are in the fifth or sixth decade of life.

Symptoms are usually mild at onset and consist of an increase in the amount of mucus in the throat and occasional sticking of solid food in the upper portion of the esophagus. As the sacculation increases in size, strangling during sleep and noisy deglutition are noted. Regurgitation of food is a disturbing symptom, and the material that is ejected at the end of the meal is usually that which was first swallowed.* When the sac becomes larger, much of the food that is eaten is regurgitated, and the patient loses weight and strength from malnutrition and loss of sleep. Sleep is interrupted because of regurgitation and aspiration of the contents of the sac. Chronic pulmonary infection frequently ensues, increasing the risk of surgical treatment.

Roentgen examination with the patient swallowing a mixture of barium will demonstrate the character of the lesion and the size of the sac. A rare complication is carcinoma in the wall of the sac, and whenever this is suspected, esophagoscopic examination is indicated. In the majority of patients esophagoscopy is unsatisfactory and unnecessary.

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* Fetor oris may be a prominent symptom.—EDITOR.

Pulsion diverticulum may also arise just above the cardia, probably as a result of mild spasm of the musculature of the cardia. Sacculation at this area may be single or multiple, and symptoms depend on the size of the diverticulum. If the sac is large, distress after meals, regurgitation of food and epigastric pain may be present. Dysphagia may be a prominent symptom. Careful roentgen study is required to differentiate diverticulum in this location from cardiospasm, diaphragmatic hernia and diverticulum of the cardiac portion of the stomach.

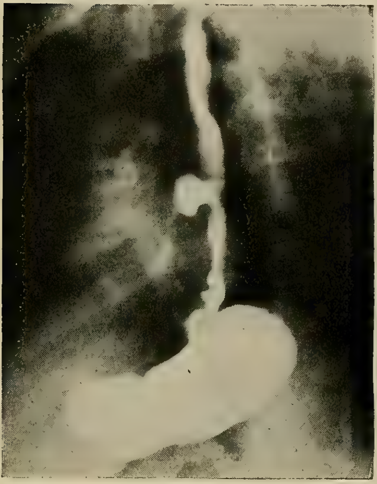

FIG. 34

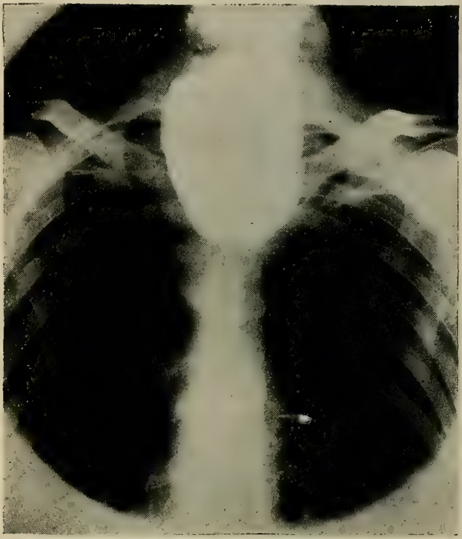

FIG. 35

FIG. 34.—Traction-pulsion diverticulum of the esophagus, resulting from associated cardiospasm.

FIG. 35.—Pharyngeal or pharyngoesophageal pulsion diverticulum.

Treatment.—*Traction diverticulum* seldom produces symptoms, and treatment is rarely required. If the diverticulum ruptures into the mediastinum with formation of abscess, surgical drainage may be indicated. When there is perforation of the diverticulum into a bronchus with formation of fistula, closure by operation may become necessary.

Traction-pulsion diverticulum does not often produce symptoms, and treatment should be directed to the lesion that produces obstruction in the esophagus distal to the sacculation.

Pulsion diverticula in the lower pharyngeal region, usually designated pharyngoesophageal diverticula, should be removed by operation in one or two stages, preferably the latter; or the sac can be fredd from its usual location, and its apex anchored in the tissues of the neck at a level higher than the mouth of the diverticulum. When the diverticulum is thus placed in a position promoting drainage and preventing entrance of food into the sac, the patient is rendered free from symptoms without the necessity for opening the esophagus with the associated risk of infection.

Operation of this type is particularly useful in old, debilitated patients, in whom complete removal of the diverticulum would be attended with considerable risk.

When there has been appreciable loss of weight and strength from starvation, the general nutrition of the patient can be improved and operation rendered less hazardous by guiding a small catheter or Rehfuss tube into the esophagus beyond the sac over a previously swallowed silk thread; fluid can then be introduced into the stomach for several days prior to operation. In case the diverticulum is in the lower portion of the esophagus, dilation of the cardia may relieve dysphagia. Introduction of a small rubber tube into the sac at night before retiring and evacuation of the food retained in the diverticulum may prevent nocturnal regurgitation and inhalation of food into the tracheobronchial tree.

HYSTERICAL AND FUNCTIONAL DYSPHAGIA

Hysterical dysphagia, or Plummer-Vinson syndrome, is characterized by difficulty in swallowing solid food, without existence of an obstructive lesion in the esophagus. It is associated with glossitis, anemia and splenomegaly. The condition is observed almost always in married women more than forty years of age, the majority of whom are edentulous and use dental plates. The Scandinavian race is particularly susceptible.

Symptoms usually begin gradually with inability to swallow pills and large pieces of meat. They are usually progressive, and dysphagia may assume ridiculous proportions; for instance, one of my patients said she was unable to eat strawberry icecream because of the seeds; another could not swallow buttermilk unless the small particles of butter fat were removed.

Anemia of the hypochromic type develops to a marked degree, probably because of nutritional deficiency. The dysphagia is thought by some observers to result from change in the mucous membrane of the mouth and esophagus associated with anemia. The tongue is red and smooth, showing evidence of atrophy of the mucous membrane, and fissures are noted at the corners of the mouth. In about one-fourth of the patients the spleen is palpable, and in some it may be greatly enlarged.

Roentgen study is usually made with difficulty because of the patient's fear of choking, and the examination may be unsatisfactory. Passage of a stomach tube for determination of the degree of gastric acidity is not advisable for all patients. Achlorhydria may be found, although this has not been noted consistently.

Esophagoscopy reveals a smooth, pale, glazed mucous membrane in the pharynx and upper portion of the esophagus, but narrowing of the lumen has not been observed. When the patient, after passage of the esophagoscope or introduction of sounds into the stomach, is assured that the esophagus is normal, dysphagia is relieved at once, and any type of food can be eaten without difficulty. Large pills will be swallowed with ease.

Treatment.—Treatment consists of assurance that choking will not occur with swallowing after the esophagus has been "dilated." After deglutition has been restored, the blood count usually returns to normal, and the enlarged spleen recedes in size. The majority of patients remain well after treatment, and in those having a recurrence of dysphagia, passage of a small sound through the esophagus will always restore the ability to swallow normally.

Another type of dysphagia that is dependent on psychic factors is known as functional dysphagia, to distinguish it from hysterical dysphagia. This is observed in both sexes and may be encountered at any age. It is not associated with anemia, glossitis or sphenomegaly. Patients note difficulty in swallowing liquid as well as solid food, and food may be kept in the mouth for a long period before swallowing is attempted. Symptoms usually result from psychic shock, and relief is obtained by prolonged encouragement. Passage of sounds is not indicated, and any type of instrumentation usually intensifies the disability. When a patient has been relieved of functional dysphagia, symptoms rarely recur.

INJURIES TO THE ESOPHAGUS

The esophagus is relatively delicate in structure, but is well protected and is not often injured by external trauma. Wounds from gunshot injuries have been observed, but stab wounds have seldom been recorded. Occasionally rupture of the esophagus follows external trauma to the thorax, even without fracture of the ribs. Spontaneous rupture may follow prolonged vomiting or excessive physical strain.

The majority of injuries to and perforations of the esophagus result from foreign bodies becoming lodged in the lumen of the tube, from instrumentation for removal of foreign bodies or from dilatation in the presence of obstructive lesions. Open safety pins and bones are a frequent cause of perforation. Simple lacerating wounds of the esophagus or even extensive ulceration associated with the presence of a foreign body usually heals rapidly after the body has been removed, unless perforation has occurred.

All instruments should be introduced into the esophagus with care. Perforation may occur from passage of an esophagoscope, and unless sounds are guided into the esophagus by a previously swallowed silk thread, attempts at dilating esophageal stricture may result fatally. Spontaneous perforation of a malignant lesion is observed rather often, and it is notable that with a thread as a guide, carcinomatous obstruction can be dilated with less than 1 per cent risk of rupture. Rupture of a benign stricture following dilation is rare.

Probangs and coin catchers should never be introduced into the esophagus, and the common practice of swallowing bread crust in an effort to dislodge a foreign body should be discouraged. Induced vomiting or forced deglutition may cause perforation of the esophagus in the presence of a foreign body.

Superficial erosion of the esophagus does not produce significant symptoms, and the soreness of the throat that follows introduction of an esophagoscope or dilating sounds usually disappears within twenty-four hours after instrumentation.

In cases of acute perforation, subcutaneous emphysema is noted in the tissues of the necl almost immediately after the injury hs occurred. Pain may be severe, and shock is pronounced. Fever is usually noted within a few hours. When perforation has occurred in the lower portion of the esophagus, pleurisy with effusion or pneumothorax with secondary infection soon becomes manifest. The left pleural space is the first to show evidence of infection. Perforation into the trachea from a malignant growth may occur without pain, shock or emphysema, the only symptom being strangulation during the swallowing of liquid.

Rupture of the esophagus may occur from many causes without fatal outcome. I have observed emphysema in the tissues of the neck without fatal result after removal of a foreign body from the upper portion of the esophagus and after dilation of a malignant stricture in any portion of the organ. The perforation was evidently not large enough to permit leakage and serious infection.

Treatment.—For perforation of an esophagus not involved by malignant growth, the advisability of surgical measures must be considered. Surgical exposure with repair of a rupture in the esophagus is a formidable procedure, and it is my opinion that supportive measures are preferable to operation. Fluid should be administered by routes other than the mouth, and sulfonamides should be given to combat infection. I have observed many patients who undoubtedly have suffered from rupture of the esophagus, in whom the infection in the mediastinum localized and drained into the esophagus with recovery.

If a patient with suspected rupture survives the accident for three or four days, water can be given by mouth in small amounts, followed by other liquids and soft food. Stricture usually results from the healing of a rupture in the esophagus, and repeated dilation may be required over a long period to restore deglutition to normal.

UNUSUAL TUMORS OF THE ESOPHAGUS

The majority of new growths that involve the esophagus are malignant, usually carcinomas, although a few sarcomas have been reported. Benign tumors occur with enough frequency to demand consideration when the patient has indefinite symptoms related to the esophagus. A small benign tumor seldom causes symptoms, because it does not involve the entire circumference of the esophagus and, therefore, does not interfere with deglutition. As the tumor becomes larger, however, it may fill the lumen of the esophagus and cause mild or moderate dysphagia. I have not observed severe difficulty in swallowing produced by benign tumor.

Mild dysphagia over a long period without progression of symptoms in a patient who shows extensive filling defect in the wall of the esophagus when examined roentgenoscopically should suggest the presence of a benign tumor. One of my patients regurgitated a pedunculated tumor of the esophagus on two occasions. When the tumor was removed, it was found to be a lipoma 11½ inches long.

Myoma, hemangioma, hemangioendothelioma, adenoma, papilloma and polyp are other tumors which have been observed in the esophagus. Diagnosis depends on esophagoscopy with removal of tissue for miscroscopic examination or removal of the entire tumor. Benign tumors in the upper portion of the esophagus can be removed by external esophagotomy. Those in other areas may be removed with a snare introduced through an esophagoscope or by electrocoagulation. Small benign tumors, such as myomas, which are not producing symptoms, do not require treatment, whereas adenomas and hemangiomas should be removed if possible, because they may become malignant.

Varices may develop in the lower portion of the esophagus in association with cirrhotic change in the liver. Although the veins may be greatly dilated and produce deformities that suggest benign tumor, they never cause obstruction to swallowing. Ulceration with severe or even fatal hemorrhage is usually the first indication of the presence of varices. Roentgen examination after ingestion of a mixture of barium may reveal deformities in the wall of the esophagus when dilated veins are present, but more often the veins cannot be demonstrated. If the veins are prominent, they may be seen on esophagoscopic examination.

Injection of a sclerosing solution into the veins through an esophagoscope has been accomplished in some cases, with fairly satisfactory results. Ligation of veins near the cardiac end of the stomach may prove to be of some value in reducing the incidence of hemorrhage.

ACTINOMYCOSIS AND BLASTOMYCOSIS

Actinomycosis and blastomycosis rarely involve the esophagus. I have observed one patient in whom esophagobronchial fistula developed during the course of generalized actinomycosis and was considered due to invasion with actinomyces. In another patient a primary lesion in the esophagus resulted from blastomycosis.

DIPHTHERIA

Stricture of the esophagus developed in two of my patients after diphtheria. Diphtheritic infection of the esophagus, however, is rare and almost always fatal.

SYPHILIS

Ulceration of the esophagus is probably frequent during the secondary stage of syphilis, but lesions of this type do not produce symptoms and are rarely observed. Gummas involving the esophagus have been reported. Syphilis may be present in patients who suffer from difficulty in swallowing from any cause, but since syphilis rarely affects the esophagus, other causes for the dysphagia should not be overlooked.

TUBERCULOSIS

Difficulty in swallowing is associated with tuberculous lesions in the hypopharynx and larynx, particularly when there is ulceration of the epiglottis. Obstructive lesions of tuberculous origin are much less frequent. Tuberculosis of the mediastinal lymphatic nodes may involve the esophagus and cause diverticula, which, in turn, may rupture into the left bronchus.

Treatment.—Treatment for tuberculous lesions in the hypopharynx and esophagus is unsatisfactory. When swallowing is painful, the spraying of the throat with a solution of cocaine or other anesthetic before meals may be necessary to permit ingestion of an adequate amount of food. In some cases gastrostomy may be indicated. When an obstructive lesion is present, dilation wisr sounds is advisable.

ESOPHAGITIS

Nonspecific inflammation is the most common lesion of the esophagus. It is present in about 7 per cent of all cases at necropsy. Definite symptoms occur in 10 per cent of cases in which a pathologic diagnosis of esophagitis is made, although diagnosis is rarely made during life. If more consideration were given to symptoms of esophagitis, diagnosis of this disorder would likely be made with greater frequency.

There are three predominating types of esophagitis: acute ulcerative, subacute ulcerative and chronic. Acute ulcerative esophagitis is that most frequently encountered. So-called peptic ulcer of the esophagus probably represents an area of acute or subacute ulceration.

The chief causes of esophagitis are prolonged vomiting and introduction of tubes into the stomach for lavage or feeding. Other factors are infection in the tonsils, teeth, gallbladder or appendix. In a few cases there has been associated disease in the brain. Surgical procedures may be a factor in the production of esophagitis, in that relaxation of the cardia may occur during anesthesia, permitting stasis of gastric secretion in the esophagus.

Pain, hematemesis and difficulty in swallowing are the cardinal symptoms of esophagitis. The pain, located substernally, is of a burning type without radiation. Swallowing intensifies discomfort, and food and alkalis do not afford relief. Bleeding may be in a large or small amount. When blood is vomited, it may be bright red or dark brown. Difficulty in swallowing in the early stages of the disease usually results from pain on deglutition. Later, actual stricture may develop from the healing of areas of ulceration.

Roentgen examination is rarely helpful in diagnosing acute esophagitis, but when healing has occurred with formation of stricture, the area of narrowing may be demonstrable. Esophagoscopy will permit accurate diagnosis of esophagitis during life; if, however, the patient is seen during the acute stage of the disease, pain may be so severe that direct examination of the esophagus may be contraindicated. When the disease becomes chronic or when a patient has unyielding gastric symptoms, esophagoscopy is advisable. Acute esophagitis should be prevented by care in passing tubes into the stomach and by control of vomiting.

Treatment.—A bland soft diet, morphine for pain and tincture of belladonna for relief of spasm of the esophagus are the chief indications in the acute stages of the disease. If the lesion becomes chronic, all foci of infection should be removed, and if stricture occurs, the area of stenosis should be dilated to restore normal deglutition. Gastrostomy may be required in a few instances before healing will take place, to provide complete rest for the esophagus.

FOREIGN BODIES IN THE ESOPHAGUS AND STOMACH

Not more than 5 per cent of lesions in the esophagus result from foreign bodies, which enter the tracheobronchial tree twice as often as they become impacted in the esophagus, their size, shape and consistency determining whether they will pass into the stomach or become lodged in the esophagus. Although foreign bodies in the esophagus are relatively infrequent, it is important that they be recognized and removed promptly. A foreign body may remain in the tracheobronchial tree for many months or years without causing death or serious disability, whereas a foreign body in the esophagus usually produces ulceration, perforation and fatal mediastinitis unless it is removed soon after ingestion. The danger of mediastinitis is increased if the foreign body is a bone partly covered with meat.

Disk-shaped objects, such as coins, buttons, tokens and washers, comprise about one-fourth of the foreign bodies encountered in the esophagus. Bones, large pieces of meat, dental plates, open safety pins and various metallic trinkets are the other articles usually swallowed (Fig. 36). Contrary to popular belief, foreign bodies in the esophagus are as frequent in older patients as in children. Adults who have had their teeth extracted and use dental plates frequently swallow bones from chicken, game or meat chops because of impairment of sensation in the mouth and inadequate mastication. Straight pins, needles and fish bones may stick in the base of the tongue, hypopharynx or tonsillar area. If they enter the esophagus, they usually pass into the stomach and through the intestinal tract without retardation.

A foreign body may become lodged at any point in the esophagus, but is seen most often just below the cricopharyngeus muscle. In the esophagus, it almost always produces discomfort or obstruction to the passage of solid food. If it is high in the esophagus or at the cardia, pain on swallowing is noted. In case of ulceration, fever is often noted, and when perforation occurs, emphysema in the tissues of the neck is usually observed.

A substance such as a piece of bone which has passed through the esophagus into the stomach may have scratched the mucous membrane in the hypopharynx, causing a sensation indistinguishable from that produced by a foreign body. In such cases one should assume that a foreign body is present in the esophagus, and esophagoscopy should be performed without delay. An area of erosion may be found in the esophagus, indicating the former presence of a foreign body, or the foreign body may be dislodged by passage of the instrument and slip into the stomach.

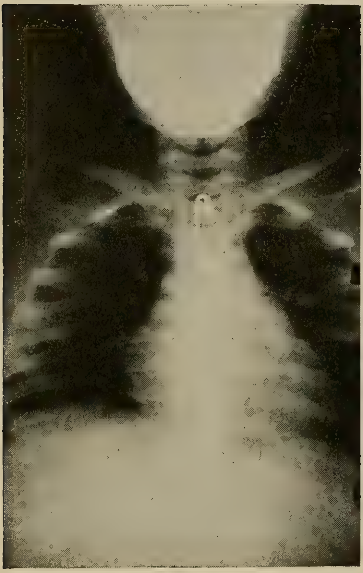

FIG. 36.—Open safety pin in the esophagus. This type of foreign body is frequently encountered.

Patients who experience the sense of a "lump in the throat" without pain or dysphagia should not be subjected to esophagoscopic examination when symptoms have been present for several months or if there is not a definite history of swallowing a foreign object. Such symptoms are usually functional and will be intensified by instrumentation.

A metallic foreign body in the esophagus is easily demonstrated by roentgenoscopy, whereas other substances, particularly bones, may not cast a significant shadow. Calcification of the cartilages in the larynx is sometimes mistaken for a foreign body by inexperienced observers. When the presence of a foreign body in the esophagus is suspected, it is unwise to administer material by mouth that is opaque to the roentgen ray in an effort to locate an area of obstruction, for it may form a coating over the foreign object and make removal more difficult. Immediate esophagoscopy is preferable when there is doubt about the presence of a foreign body.

Treatment.—The majority of foreign bodies can be removed with reasonable safety through the mouth by esophagoscopy. When a foreign body in an adult is large or when perforation is suspected, esophagoscopy should be done under deep ether anesthesia; otherwise, local anesthesia may be employed. In children, however, general anesthesia is recommended for removal of a foreign body by esophagoscopy.

When difficulty is experienced in identifying the point of an open safety pin, pushing the pin into the stomach is the advisable procedure. From there it will usually pass through the intestinal tract without retardation. A complete dental plate may occasion great difficulty in removal. Manipulating it into the stomach may be advisable, and, if necessary, it may be removed later by laparotomy. The majority of foreign bodies that enter the stomach continue uninterruptedly through the intestinal tract, and operation is seldom advisable. When a foreign body is present in the stomach or intestines, the use of laxatives is not advisable. Maintenance of a normal diet is preferable to ingestion of a large amount of bulky food.

FISTULA FROM THE ESOPHAGUS INTO THE AIR PASSAGES

A fistulous opening from the esophagus into the air passages occurs frequently with carcinoma which begins in the esophagus, but rarely does it occur with primary malignant disease of the tracheobronchial tree. Developmental defects in the esophagus and air passages are also associated with fistula. Fistula may be caused by tuberculosis, actinomycosis or syphilis, or it may arise from ulceration of a foreign body from the esophagus into the air passages, or *vice versa*. A small traction diverticulum of the esophagus may become infected, form an abscess in the mediastinum and rupture into a bronchus. When the patient recovers from infection of this type, a fistula usually remains.

Symptoms of fistula depend on the size of the opening into the tracheobronchial tree and the type of lesion responsible for the communication. With congenital abnormality with fistula, symptoms begin immediately after birth. When fistula results from malignant disease, dysphagia is usually present for several weeks or months before perforation occurs. I observed one patient, however, in whom perforation developed one week after dysphagia began.

A fistula may be disclosed by roentgen study after ingestion of a radio-opaque mixture, preferably iodized oil. Obstruction high in the esophagus may cause an overflow of the material into the pharynx, which may be mistaken for fistula. Strangulation after the swallowing of liquid is always suggestive of fistula. When such an opening is present, the patient should not be allowed to swallow a thread for dilation. The thread invariably passes through the opening into the trachea or a bronchus and is coughed up and reswallowed. Finally, many strands become entwined around the esophagotracheal septum and make removal of the thread difficult. Fistula from a congenital defect is seldom compatible with life, and operative treatment has not proved successful.

Perforation associated with inflammatory lesions may not cause serious symptoms if the opening is small. In a few cases healing has followed local treatment through an esophagoscope. When perforation into the air passages has resulted from malignant disease, treatment is unsatisfactory. Gastrostomy may provide partial relief from strangulation, but almost all patients die soon after a tube is inserted into the stomach. Intubation of the esophagus in cases of fistula from carcinoma is not often helpful, although with fistula resulting from other lesions it may promote healing.

EXTRAESOPHAGEAL LESIONS CAUSING DYSPHAGIA

Difficulty in swallowing may be produced by a number of lesions not primarily esophageal.

Herniation of a portion of the stomach through the esophageal hiatus in the diaphragm is a frequent cause of dysphagia. The hernias are of two types, the paraesophageal variety and congenital shortening of the esophagus with hernia. In the paraesophageal type, the esophagus is of normal length, but the esophageal hiatus is larger than normal, and a portion of the cardiac end of the stomach protrudes into the thorax, usually on the left side. Dysphagia may be caused by pressure of the herniated portion of the stomach on the lower end of the esophagus or by actual organic stricture.

When paraesophageal hernia is demonstrated, the esophagus should be investigated before operative treatment is employed. In many cases of paraesophageal diaphragmatic hernia, dysphagia may be relieved by passing a sound, size 60 French, into the stomach.

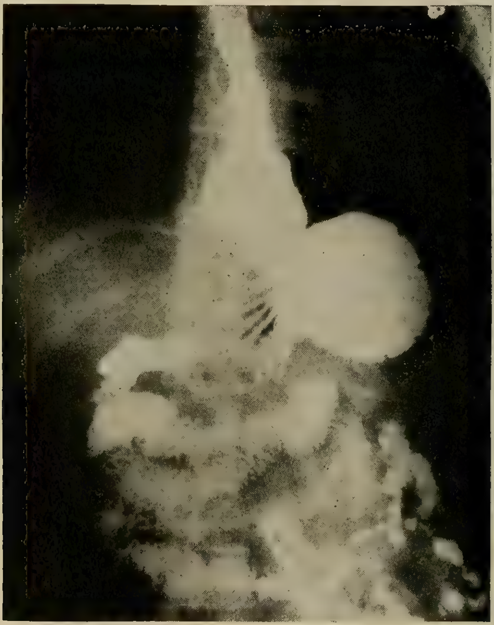

Fig. 37.—Congenital shortening of the esophagus, with herniation of a portion of the stomach into the thorax.

In congenital shortening, the esophagus is about 2 inches shorter than normal, and a portion of the cardiac end of the stomach is found in the thorax (Fig. 37). Usually dysphagia is an outstanding feature. Narrowing or actual stricture of the esophagus at the esophagogastric junction is responsible. This narrowing may result from ulceration and healing, with contraction of the lumen of the esophagus. Hemorrhage is frequent. Dysphagis is usually relieved by dilation of the area of stenosis.

Neurologic lesions may cause dysphagia. Myasthenia gravis is associated with inability to chew and swallow normally, and aspiration of food into the tracheobronchial tree is a frequent cause of fatal pneumonia. When dysphagia becomes marked in a patient suffering from disturbance in innervation in the muscles of deglutition, he should be fed by means of a small rubber tube introduced into the esophagus.

Injury or infection of a recurrent laryngeal nerve is often associated with a mild degree of dysphagia, particularly inability to swallow liquid. Strangulation and regurgitation of fluid through the nose are characteristic of dysphagia, caused by a disturbance of innervation.

Growths in the pharynx frequently interfere with swallowing, and inflammatory lesions in the mouth, hypopharynx and larynx may cause painful deglutition. Tumors of the mediastinum do not cause dysphagia unless there is compression of the esophagus, occasionally observed with metastatic carcinoma. Tumors of the thyroid gland may cause difficulty in swallowing, especially if they are malignant. Fixation of the thyroid gland from a tumor or inflammation without reduction in the lumen of the esophagus may cause dysphagia. Spinal deformity, Pott's disease and exostosis from the hyoid bone or spine have been described as other causes of difficulty in swallowing.

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CHAPTER VI

THE PHYSIOLOGY OF THE STOMACH

In the normal human subject the shape (and tonus) of the stomach as seen with the *x*-ray varies considerably. Stomachs have been classified as hypertonic (hypersthenic), orthotonic (sthenic), hypotonic (hyposthenic) and atonic (asthenic).[69] According to Barclay, [20] the most common type of stomach is T shaped, of which the fish-hook and steer-horn types are variations; the transversely placed steer-horn stomach is seldom found in females, but is common in short stout males with prominent abdomen who habitually overeat (pyknic type); the long type is met in tall thin women who eat sparsely. Barclay[20] expressed preference for classifying normal stomachs as long and short according to the degree of tonus; this tonus may change from day to day, thus altering the appearance (*vide infra*). During laparotomy he often saw a stomach of entirely different shape from that seen radiologically before operation and varying from the tightly contracted to the large and flabby; these changes he attributed to the effects of anesthesia, surgery, etc. The tonic condition of the stomach is reflected by its emptying time: the more tonic stomach empties faster than the less tonic one.

The stomach consists of four parts: cardia, main stomach (fundus, corpus ventriculi), pyloric antrum (canalis egestorius) and pylorus.

Cardiac Sphincter.—Although anatomically no distinct sphincter of the cardia can be found, one is forced by experimental and clinical observations to assume the existence of a fuctional sphincter. The cardia and stomach relax during the process of swallowing.[42] Contractions of the circular musculature of the cardia have been seen after vagotomy or abdominal visceral stimulation.[45] The esophageal persitalsis of swallowing is usually not continued by the gastric musculature, but stops at the cardia. Normal persons sometimes experience a painful cardiospasm when drinking cold liquids. Knight and Adamson[126] have obtained experimental evidence on the existence of a true sphincteric mechanism at the cardia, relaxed by vagal and contracted by sympathetic stimulation. Finally, the disease called cardiospasm has contributed much to the study of a sphincteric cardiac mechanism. Much evidence accumulated recently shows that cardiospasm not produced by reflexes from distant diseased organs (gall-bladder with stones, *e. g.*) or other foci of irritation, or by organic disease of the esophagus or cardiac part of the stomach is related to damage to vagus fibers or to damage and loss of ganglion cells of the myenteric plexus of the esophagus at the cardia.[137] Hurst and Perry[107] called the disease "achalasia" of the cardia; the theory of Hurst and associates[106] proposed that through destruction of the parasympathetic myenteric plexus the sympathetic fibers of the cardiac portion of the esophagus act unopposed and keep the cardia closed, so that the normal opening reflex of the cardia cannot take place at swallowing (Einhorn;[63] Rolleston[203]), and dysphagia occurs, with gradual dilatation of the esophagus. In the cat, after section of the splanchnic nerves the cardia lost its power to open reflexly,[123] comparable to the tonic "locking" of certain muscles in mollusks after section of their motor nerve. The afferent and the efferent part of the reflex arc for the opening of the cardia seem to run in the vagi. The term "achalasia" is certainly better than "cardiospasm," although it may not cover the entire field of clinical experiences: it is hardly believable, for instance, that degenerative changes in the myenteric plexus of the esophagus may be held responsible in cases of functional obstruction of the cardia during hysteria or reflex disturbances from the abdominal cavity, which often disappear after operation (cholecystitis, appendicitis, etc.). Vitamin B_1 may play an important role in the maintenance of the normal plexuses, and avitaminosis B may lead to their degeneration.[66]

The Fundus.—The fundus is capable of great dilatation in order to receive ingested food, which is stored in it and slowly penetrated by the digestive juice. Similar to the urinary bladder, the normal fundus has the property of tonic adaptation to its contents, *i. e.*, its musculature contracts tonically around the volume of food ingested (except in the ptotic stomach). When food is tasted or swallowed, the normal tonic stomach relaxes immediately (receptive relaxation).[42] In certain abdominal diseases this reflex may be reversed, giving rise to distress.[262] Appetite increases the tonus of the normal stomach.

The Pyloric Antrum.—The pyloric antrum is a powerful muscular organ. According to roentgenologic and gastroscopic observation it has two sphincters, which are able to separate this part from the fundus and duodenum.[215] The sphincter antri pylorici is usually of ropelike appearance; it seems to occlude the fundus while liquid or semiliquid food is passed or ejected into the duodenum. It may also be responsible for the occasional differences in acidity of the gastric juice at different levels of the stomach.

The Pyloric Sphincter.—This is a definite muscular entity, developed from the muscularis propria and submucosae of the antrum. It has little or no muscular contiguity with the duodenum, but the intrinsic nerve plexuses of the stomach continue through it into the duodenum. The mechanism of gastric emptying through a normal pylrous has been discussed for hundreds of years[228] and is not yet understood completely (see "Digestion"). ⁂Sphincter closure is under sympathetic and sphincter opening under vagus control. This is just opposite to the usual nervous control of the gastrointestinal smooth muscle, but, as discussed under "Innervation of the Stomach" (*vide infra*), there are significant exceptions.

Upper Part of the Stomach.—This part between the cardia and the pylorus (their shortest connection is called the *gastric furrow*, or canalis gastricus), has less folds, a thinner mucosa and a shorter submucosa than the fundus. The theory that most of the food and liquid, and presumably rough particles, has to pass along the lesser curvature on its way to the duodenum is no longer tenable.[4] Circumstantial evidence for this assumption was found in the shape of the crater of many ulcers of the lesser curvature (overhanging steep edge toward the cardia and slow slope toward the pylorus); however, the normal direction of peristaltic waves is toward the pylorus, and this in itself seems sufficient to explain the peculiar shape of ulcer craters. At *autopsy* or after resection the gastric mucosa appears reddish and shows many rugae. At gastroscopy a different picture is seen. The pyloric antrum shows few folds. It seems that in the dead organ the more powerful pyloric musculature contracts, thus causing folds (rugae) to appear. The musculus sphincter antri, mentioned previously, is usually not seen in the dead organ; it is seen rarely at *x*-ray examination and nearly always at gastroscopy. Thus gastroscopy is teaching us new facts about the functional anatomy of the stomach (Schindler, 1936,[215] 1937[216]).

Surface of the Stomach.—This is lined with a simple epithelium of mucus-secreting cells. The cardiac glands are mucous glands. They are considered to be retrogressive structures derived from fundus glands by the diappearance of their more highly specialized cellular constituents. The cardiac glands extend between 5 and 43 mm. into the stomach.[23] The area of transition between pyloric and body glands is usually more abrupt near the incisura angularis, while on the greater curvature the transition is more gradual, beginning anywhere between the knee and the pylorus. The glands of the body contain mainly mucous neck cells, chief or pepsin cells and parietal cells. Parietal cells are distributed uniformly in the body, with a slight decrease in number at the lesser curvature and a definite decrease in the fundic and cardiac regions (Berger;[25] Maximow and Bloom[148]). The glands of the pyloric mucosa contain only one type of cells, resembling the mucous neck cell of the body or the cells of Brunner of the duodenum. Their secretion contains alkaline fluid and mucus only. After gastritis the entire gastric mucosa or parts, islands, may contain only such mucous cells. Occasional islands of mucous cells found in so-called normal stomachs and regarded by some as ectopic duodenal or pyloric mucosa probably represent remnants of localized gastritis.

Blood Supply of Stomach.—The blood supply of the stomach is extremely efficient. The submucosal and intramuscular bloodvessels anastomose to such a degree that it is difficult to deprive any part of the stomach of its blood supply by simple ligation of the bloodvessels leading to it.[26] It seems that the distal part of the lesser curvature has no anastomoses between the end-arteries or less than the rest of the stomach, but this is contested. It has been assumed that the veins of the submucosa are prone to functional obstruction, stasis, etc., by contractions or a rise in tonus of the stomach as well as by temporarily increased pressure in the portal vein; mucosal hemorrhage has been attributed to this peculiarity.

INNERVATION OF THE STOMACH

Gastric peristalsis is myogenic, not neurogenic. Rhythmic muscular activity seems to be an inherent quality of smooth muscle, and the function of the intrinsic and extrinsic gastric nerves seems to be that of coördination of distant parts of the stomach and of the body as a whole organism.[5] Besides coördination through the nerves there is coördination through the blood (*vide infra*).

Intrinsic Nerves.—The intrinsic nerves of the stomach consist of the intramuscular and the submucous plexuses of ganglion cells and nerve fibers. The number and size of the ganglion cells in the plexuses vary in the different parts of the stomach; in the myenteric plexus in the pyloric region they have been described as particularly large.[25] The efferent fibers of the vagus seem to effect synaptic connection with neurons in the ganglions of the plexuses, and some of their effects on the stomach seem to be exercised by this route. The efferent sympathetic fibers do not seem to form such connections, but run through the ganglions to their effector cells. Afferent fibers of the vagus and sympathetic nerves may travel directly through the ganglions of the plexuses without synpatic connection. Many fibers from the plexuses ramify among the muscle fibers, glands and epithelium of the stomach. It is not clear as yet whether efferent vagus and sympathetic fibers supply separate systems of nerve nets or neurons in the plexuses.[132] The stomach is to a great extent an autonomous organ, and most of its functions continue after complete denervation. A gastric pouch or a whole stomach of a dog transplanted into the mammary glands or subcutaneously into the neck or viviperfused will continue to exhibit hunger motility parallel to that of the main stomach and secrete acid when histamine is administered or a meal is eaten. It has been suggested recently that reflex arcs may exist between the myenteric plexus and the celiac ganglion; that reflexes through this path are independent of extrinsic nerves, and that duodenal regurgitation into the stomach may be regulated through these channels.[133]

Extrinsic Nerves.—The extrinsic nerve supply to the stomach consists of the vagi and of sympathetic fibers (from the splanchnic nerves and from the celiac plexus) accompanying the vagi or the arteries or going through the lesser curvature.[37] The area around the lesser curvature has the greatest supply of vagus fibers. Section of the vagi at the cardia will lower motility and emptying time for a while, but these will return to normal soon. It has been shown recently[150] for the dog that while vagotomy does not alter the emptying time for liquid foods, that of solid and semisolid foods is lengthened considerably for an observation period of five months.

The end-arborizations of the vagi in the walls of the stomach do not act directly on the cells (or ganglion cells) when impulses reach them. A mediator substance is liberated, which in turn acts on the end-organs; this substance is acetylcholine, of which a precursor seems to be available at the nerve endings. It is destroyed rapidly by a ferment present in blood and tissues and in higher concentration at the nerve endings, acetylcholine esterase. The origin of this ferment is not known, although we[81] found large amounts in the external secretion of the pancreas. The sympathetic branches supplying the stomach act in a similar way, with the difference that the intermediary substance is an epinephrine-like compound (Cannon's adrenine); this compound is also destroyed by a ferment (tyrosinase). Acetylcholine diminishes the blood flow through the stomach.[163] Acetylcholine produces intense motility of the stomach when injected in amounts so large that not all of it is destroyed by the esterase of the blood; administered orally it is not effective. Synthetic choline esters which are not hydrolyzed as rapidly as acetylcholine by esterase have been produced. These compounds, therefore, are much more effective than acetylcholine in producing gastrointestinal motility and act also when given orally; acetylbetamethylcholine chloride (mecholyl) is the best known of these esters; in consequence of its cardiovascular effects it has to be used with great care.

If the esterase is inhibited temporarily from destroying acetylcholine formed at the neuromuscular junction, muscular activity of the stomach is greatly increased. The main drugs having this property are physostigmine (eserine) and its derivatives; besides its inhibitory action on esterase activity and the resulting greater effectiveness of vagus activity, physostigmine has a direct effect on the muscle cells. Because physostigmine has a number of undesirable by-effects (sweating, salivation, lacrimation, abdominal cramps, cardiovascular collapse, etc.) efforts have been made to obtain a more suitable similar synthetic drug; the dimethyl carbaminic ester of m-oxyphenyltrimethylammonium methylsulfate (prostigmine) has the esterase-inhibiting effects of physostigmine without most of its undesirable by-effects. Prostigmine resembles physostigmine also by having a direct effect on smooth muscle, besides inhibiting the destruction of acetylcholine (Meyer and Necheles,[156] Schwartz, Reingold and Necheles[223]). Acetylcholine in combination with eserine or prostigmine has been found by us to be effective in raising the tone and activity of the stomach and intestines (Frank, Zimmerman and Necheles;[74] Zimmerman, Frank and Necheles;[275] Schwartz, Reingold and Necheles;[223] Necheles[168]).

Drugs.—Atropine and its derivatives act on the gastric musculature by blocking the effect of acetylcholine on the muscle, bloodvessels and secretory cells. In the presence of atropine, vagus stimulation still liberates acetylcholine, but the motor effects of the acetylcholine are either partially or completely depressed. The variability of atropine inhibition in different parts and in different states of the gastrointestinal tract is not well understood as yet (for discussion, see Henderson and Sweeten[95]). Small doses of atropine have been reported to increase gastric motility, and large doses to diminish it.[9] Likewise, its effect on gastric secretion is not uniform, but depends on the secretory stimulus, the presence of a duodenal ulcer, etc. Large doses of atropine are necessary to affect acidity markedly; fluid secretion usually is diminished more than acid secretion.[95] Histamine secretion is not affected much by atropine. Following abdominal operations, a "traumatic secretion" has been observed.[111] Atropine delays the emptying of the human stomach (Herrin[98]). A new synthetic drug, diphenylacetylaminodiethanol hydrochloride (trasentin), acts like atropine in regard to acetylcholine, but has a direct, relaxing effect on smooth muscle besides, similar to that of papaverine (Necheles *et al.*;[178] Spier *et al.*[235]). Benzedrine has been recommended[160] to relax the pyloric sphincter. We[205] have found the opposite effect. Adrenalin and ephedrine are able to depress gastric motility and secretion.[196] Smoking tobacco reflexly depresses the hunger motility and tends to depress secretion and emptying of the stomach.[220] Sodium nitrite was found to relax and to delay emptying of the human stomach,[232] but nitrites have less effect on cardio- or pylorospasm.[21] Digitalis and bile (dehydrocholic) acid shortened the emptying time of a barium meal in normal young human subjects (Tumpeer;[246] Tumpeer and Phillips[247]). Bisgard and Johnson[27] have described the effects on the stomach of anesthetics and of drugs ised in connection with anesthesia.

Stimulation of the Gastric Vagi.—This is followed by contraction and motility of the stomach when its tonus is low, but by relaxation when its tonus is high. Stimulation of the splanchnic nerves is usually followed by relaxation of the stomach; in rare cases, however, contractions may be evoked. The innervation of the cardiac (*vide supra*) and pyloric sphincters is distinctly different from that of the rest of the stomach. Both are usually closed by stimulation of the sympathetic nerves and relax on stimulation of the vagi. Exceptions have been described by Carlson *et al.*[46] and by others. P. and T. Klee[122] experimented on the cat and found that splanchnic stimulation relaxed the stomach but contracted the pyloric sphincter. Section of all sympathetic fibers to the stomach was followed by maximal increase of the tonus of the pyloric antrum (similar to that observed in nicotine poisoning). This can be explained as the effect of unopposed vagus action. This observation explains why pylorospasm is often affected beneficially by atropine, namely, when the pyloric antrum, which is under positive vagus control, is contracted. Injection of epinephrine produces a transient drop of tone and cessation of gastric motility; the same effect is produced by stimulation of the adrenal medulla through its splanchnic innervation. Nicotine is known to effect an outpouring of epinephrine from the adrenal glands; in high doses its direct muscular effect seems to prevail, thereby producing muscular activity of the stomach.

GASTRIC MOTILITY

The mucous membrane of the stomach (and intestine) has its own motility due to its muscularis mucosae, independent of the muscularis propria, and is able to form an inner relief which may be entirely different from the outer shape of the organ (Forssell[72]). This fact must be remembered in the interpretation of x-ray pictures of the gastrointestinal tract.

Gastric movements can be divided into interdigestive, or hunger, motility and digestive motility. Both have been well described by Beaumont,[22] Cannon,[42] Carlson[43] and others.

Interdigestive, or Hunger, Motility.—Small tonus waves run over the stomach at a rate of about three per minute. Superimposed on these are the hunger contractions, which occur at a rate of about two per minute. Periods of hunger contractions vary in character according to the degree of hunger and the general condition of the subject. Short periods (six to twenty minutes) begin with feeble contractions, which increase gradually and then decrease and wane off. Long periods (thirty to ninety minutes) begin with weak contractions with long intervening pauses. The contractions increase, and the pauses shorten, until a climax is reached, with powerful and rapid contractions which may fuse into a tetanic contraction at the end of the period, which is always abrupt. The tetanic contraction usually lasts two to five minutes, but periods of ten to fifteen minutes have been observed. The tetanus-like end of a hunger period is characteristic of vigorous young persons. The periods of relative quiescence between hunger periods vary from one-half to two and a half hours. Less typical periodicity can be observed.[43] The large hunger contractions, the subtetanic especially, are felt by the subjects as hunger pangs; this has been proved by simultaneous balloon and x-ray observations and signals from the subject. Appetite seems to depend largely (but not entirely) on gastric tonus and on hunger motility, and therefore, as a rule, the subject with a tonic stomach has a good appetite, while among subjects with hypotonic stomach one finds the greatest incidence of diminished or absent appetite. Not all peristaltic waves run from the cardia to the pylorus. Many of them end before or at the pyloric antrum. More powerful ones proceed to the pyloric sphincter. Some begin in the pyloric antrum. Rarely a peristaltic wave continues into the duodenum. One reason for that may be that the muscular continuity between pylorus and duodenum is rather irrelevant.

Digestion.—During digestion, peristalsis is not as marked as during hunger. Forceful churning movements, as described by Cannon[42] for the cat, are not usually seen in the normal human stomach. From these observations it is clear that a stomach can be put at rest not by fasting, but by frequent small meals, which change its strong hunger contractions into the more shallow digestive peristalsis. The hypertonic stomach has less peristalsis than the average J-shaped one and may hardly show any at all; the least of all is seen in the ptotic stomach.[20] In headaches, emotional upsets, etc., digestive peristalsis is suppressed; the same was observed[20] in diarrhea. Roentgen observations[20] tend to show that ejection of food into the duodenum is produced more by the gastric tonus than by peristalsis, pyloric control or the reaction of the food. Carbohydrates leave the stomach fastest, proteins slower and fats slowest.[42] The activity of the pyloric sphincter is governed by a number of factors. The former assumption of a simple pyloric reflex activated solely by the presence of hydrochloric acid in the duodenum and solid food in the stomach is no longer tenable. Liquids may leave the stomach in a few minutes; milk stays longer, because it is coagulated by rennin and/or pepsin. Solid foods seem to produce closure of the pylorus when they enter the pyloric antrum.[42] The most effective regulating mechanism for gastric emptying seems to consist in the presence of digested food and acid in, as well as in slight distention of, the duodenum, which are mediated by reflex arcs between the duodenum and stomach (enterogastric reflex[240]). The presence of hypertonic solutions in the upper part of the duodenum seems to inhibit gastric emptying.[78] This reflex acts less through closure of the pylorus than through inhibition of gastric motility.[241] Fat or dextrose solution in the stomach does not inhibit gastric motility or produce closure of the pylorus; only after some of it has entered the duodenum is gastric motility inhibited, while the pylorus relaxes.[195] Only organic fats or oils, fatty acids and soaps have such effect; mineral oils not. Part of this phenomenon, or rather its first phase, may be due to a nervous reflex;[194] most ot it seems to be due to liberation in the upper part of the intestine of an inhibitory substance, called enterogastrone by Lim. I have recently found a similar body in human urine in rather large quantities and this has been confirmed by others. Since, as I shall point out later, this substance also inhibits gastric secretion, we may be dealing with an important humoral mechanism (Necheles, 1937,[163] 1938[164]). The failure of a duodenal mechanism to react with the acid gastric juice and thus to effect a normal control of gastric secretion and motility has been assumed to explain the abnormal gastric motility and secretion often seen in patients with duodenal ulcer.[230]

Hormones.—Among the hormones affecting gastric motility, insulin and pituitrin are important. Insulin increases gastric motility and secretion and this is one of the reasons why it has been used to raise appetite and make patients gain weight. Recently my associates and I found that in dogs insulin may produce inhibition of gastric secretion and motility.[174] Insulin does not exert a direct effect on the stomach, but acts on the vagus centers, from which impulses are transmitted to the stomach by way of the vagi. LaBarre has shown that the effect of insulin on the stomach is abolished after section of the vagi. Injection of dextrose abolishes the hunger motility evoked by insulin but not the ordinary spontaneous hunger contractions. Insulin, therefore, acts on the stomach indirectly, by stimulating vagus centers by hypoglycemia. On the other hand, it seems certain now that the normal spontaneous hunger contractions of the stomach are not due to a possible hypoglycemia of hunger, mainly because no significant variation of the blood sugar level has been found during pronounced hunger contractions in man; intravenous dextrose therapy does not abolish them, and they still persist in completely denervated stomachs. I may conclude, therefore, that spontaneous hunger motility is due to other, yet unknown reasons.

Some persons experience extreme hunger shortly after a large meal. This may be due to the hypoglycemic phase following hyperglycemia from over-ingestion of carbohydrates, *i. e.*, over-stimulation of the pancreas, and is appeased by the eating of carbohydrates or by administration of atropine.

The secretions of the posterior lobe of the pituitary gland produce vigorous contractions of the intestines, but apparently not of the human stomach (Necheles and associates;[171] Van Dyke[250]). Both pituitrin and pitressin produce vasoconstriction and diminution of the blood flow through the stomach and, consequently, a relative anoxemia. As shown recently by Lim and his associates[141] and by Necheles and Neuwelt,[177] pituitrin (the vasopressor and the oxytocic fraction) is liberated after stimulation of the proximal end of a vagus nerve. This indicates the existence of a reflex secretion of pituitrin; if this can be proved to occur in man under normal conditions or in disease, an important mechanism will have been discovered. The vagus innervates so many abdominal organs that a disturbance occurring in any one of them may lead to reflex secretion of pituitrin, which in turn will act on the stomach and other organs of the gastrointestinal tract. Irritation of these latter organs may in turn set up another vagus reflex leading to secretion of pituitrin, and a vicious circle may be started.[172] Another important angle of this reflex will be discussed under gastric secretion. Progestin did not affect human gastric emptying time.[231]

Vitamins.—Avitaminosis B in dogs is followed by anorexia and gastric atony. Feeding of vitamin B complex restored normal conditions.[52] Rats kept on a B_1-deficient diet showed progressive gastrointestinal hypotonicity, dilation and stasis. Gastric retention was present. This was not due to loss of weight merely, as controls showed.[79] In human beings with abnormally long emptying time the period was shortened by administration of vitamin B_1, but in normal subjects or in patients with short emptying time, no change occurred.[274]

Avitamosis A led to anorexia which was not related to ulceration of the mucosa of the mouth or pharynx. Gastric emptying time was prolonged in most dogs, but in a few animals it returned to normal, although the avitamosis progressed.[99]

Gastric Pain.—Gastric pain is transmitted to the brain mainly by way of the sympathetic nerves. Various conditions may produce stomach pain. The one which has drawn most attention is gastric ulcer. The theory that this is due to hydrochloric acid acting on the surface of an ulceration and on the nerve endings does not stand up to experimental investigation on patients and does not seem to hold good for the majority of cases. The assumption (Meyer *et al.*;[155] Kinsella[120]) that it is due to edema in and around the ulcer, with consequent compression, asphyxia and tension on nerve endings, especially during gastric motility, as well as to inflammatory processes demonstrated in the nerve fibers in the ulcer area, seems to be supported better by clinical and experimental observations. In a subject with a wide gastrostomy Wolf and Wolff[271] observed that pain followed distention of the stomach or vigorous gastric contractions. Pricking or pinching the gastric mucosa failed to induce pain unless the mucous membrane was congested and edematous. Another painful condition of the stomach occurs in acute superficial and in chronic hypertrophic gastritis, where the same processes as in ulcer may explain the causation of pain. To the same class may belong also gastric pain and discomfort occurring in allergic diseases. Moutier has described gastroscopic observations of such conditions, in which the gastric mucosa offered much the same appearance as the skin, with allergic swelling and blisters. Cardiospasm is accompanied by pain; this probably is due to distention of the esophagus and to strong muscular contraction of the cardia, with a direct effect of pressure and anoxemia on nerve endings. The pain often accompanying pylorospasm probably also results from pressure and anoxemia in the pyloric musculature, if not from accompanying gastritis.

We[208] have shown that oil of peppermint relaxes the pyloric sphincter. Not only is the emptying time after a meal shortened after administration of small amounts of that substance, but the disturbing pylorospasm which often follows ingestion of a barium meal is relieved nearly immediately. Our results have been criticized recently by Van Liere and Northrup[251] and by Stickney,[238] who assumed that we had employed too large doses of oil of peppermint. This can hardly explain, however, the effects of peppermint candy—and the negative results in controls—reported by us. A fast method of relieving pylorospasm is to let the subject inhale some amylnitrite. Morphine produces spastic contraction of the pyloric antrum[88] and increase of gastric acid secretion.

Pyrogens.—We[168] have been able to demonstrate that doses of various pyrogenic substances, so small as not to affect rectal temperature in the dog, may depress gastric motility and secretion immediately and often for prolonged periods. We believe that these results are applicable to man, and that dyspepsias during and after various diseases with or without fever may be explained by these findings.

Vomiting.—Antiperistalsis of the stomach occurs with pathologic conditions, especially when the duodenum or the biliary tract is irritated; it may occur with most disturbances in the abdominal cavity. The nausea and vomiting in many acute infectious diseases may be due to an accompanying acute gastritis.[67] Vomiting accompanying diseases of the brain and meninges is due to stimulation of the vomiting center by nervous reflex or by intracranial pressure. Vomiting is a complex mechanism, coördinated by a center in the medulla. The diaphragm and the muscles of the abdominal wall seem to be more important in vomiting than the antiperistalsis of the stomach. During nausea the swallowing of saliva may not be of much help, because saliva and regurgitated bile stimulate gastric secretion.[188] Artificially, vomiting can be elicited easily in three ways: (1) stimulation of the pharynx, the old method of the Romans of getting ready for another meal; (2) stimulation of the gastric mucosa by weak corrosive agents like copper sulfate (the irritation of the gastric mucosa provokes the vomiting reflex); (3) chemical stimulation of the vomiting center. Emetine and apomorphine are the two most effective drugs evoking the central reflex directly. While apomorphine is fairly specific in its excitatory action on the vomiting center, no drug is known as yet that possesses as specific an effect in the opposite direction, *i. e.*, in suppression of the vomiting reflex. Finally, in pathologic vomiting psychic causes of aggravation never should be overlooked

Reflexes from the labyrinth to the stomach and intestines have been described in man and in animals. The initial gastric contraction and pyloric closure following caloric and galvanic stimulation of the ear (inner and outer) are due to stimulation of the trigeminal nerve and the auricular branch of the vagus; the impulses from the labyrinth produce nausea due, apparently, to antiperistalsis in the duodenum. The impulses from the labyrinth to the stomach are entirely depressive; gastric hunger contractions are inhibited, and when nausea appears, a marked decrease is gastric tonus regularly occurs.[136] These reflexes, together with visual disturbances following abnormal stimulation of the labyrinth, play a role in sea and air sickness.

Central Nervous System and Stomach.—A few facts about the relation between brain and stomach are known. Lesions in certain areas of the frontal lobes are often accompanied by ravenous appetite and bulimia. Lesions in the midbrain near the anterior part of the infundibulum of the hypophysis are followed by atony of the stomach, while lesions near the posterior part are followed by gastric hypermotility. These effects are transmitted through the sympathetic and vagus nerves, respectively. Section of either of them abolishes the effect of the respective lesion of the hypothalamus. Besides these motor effects, mucosal hemorrhages occur in the stomach when the anterior area is damaged, and ulcerative lesions, when the posterior area is affected. Again, these effects are abolished by section of sympathetic nerves and vagi, respectively. These experimental observations, together with clinical and pathologic data, point to the existence of separate sympathetic and parasympathetic centers in the midbrain. These centers seem to be in a kind of balance, which is influenced by cortical, thalamic and afferent processes. The presence of a lesion or destruction of one of them will be followed by unopposed effects of the other one, as indicated by atony and hemorrhage in one case and hypermotility and ulcerations in the other. Since cortical stimuli may be inhibitory as well as excitatory and because only a small area of one center may be affected by cortical inhibitory or excitatory impulses, a variety of patterns of gastric responses may arise. Therefore, the concept of sympathicotonus and parasympathicotonus should be replaced by the concept of autonomic imbalance, or, better, autonomic dyssynergia (Necheles[165]), which is much broader in its applicability. Autonomic imbalance is considered by a number of investigators to exist in most patients suffering from peptic ulcer (Fulton[76]).

Clinical Tests of Gastric Motility.—While the balloon method of recording gives a fairly good picture of gastric motility, it seems to be too difficult and time-consuming for routine clinical use. The integrated motility of the entire organ can be tested fairly well by measuring gastric emptying time fluoroscopically. It would be good if one type of meal were used everywhere, so that data could be compared on a large scale. Since nausea delays emptying considerably, the meal should be palatable. Therefore the smallest possible amount of barium should be used, together with a flavor, and a small amount of milk for better suspension of the barium.

Since fresh milk varies too much in its composition, a standard whole milk powder is preferable.* There is no "average" emptying time of the human stomach, but it varies with age, sex, habitus (*i. e.*, type of stomach) and, of course, with the type of meal employed. So far, each clinic, more or less, has its own standards for each type of stomach. Small variations in the size of the meal do not affect emptying time significantly. If the size of a meal is increased two or three times, gastric emptying time may be increased 17 or 38 per cent, respectively (Van Liere *et al.*[254]). If standardization of the barium motor meal could be accomplished, the use of a unit amount of a standard meal per kilogram of body weight or per square meter of body surface might be advisable

The more a patient is starved, the faster the initial emptying of the stomach will take place.[20]

A simple method of testing for gastric retention is to let the patient eat, at 10 P.M. of the day preceding a test meal, 50 raisins with seeds, currants, some uncooked rice or 6 dried prunes. A few seeds or shreds of prune in the aspirated gastric juice mean nothing, because some particles are usually retained in the folds of a normal stomach. The finding of many seeds or shreds of prune, however, is an indication of serious delay in gastric emptying. Emptying time has been measured by estimating the amount of solid material in the stomach at regular intervals after an Ewald meal.

Effect of Gastrointestinal Motility on the Electrocardiogram.—Tumpeer[246] and Tumpeer and Phillips[247] have demonstrated that hyperperistalsis of the stomach and of the intestine may produce considerable irregular shifts in the base line of the electrocardiogram. "Electrogastrograms" were also taken by these authors and by others,[5] but this method has not found clinical application.

GASTRIC SECRETION

Topographically, a small zone at the cardia and one at the pylorus secrete a small amount of alkaline matter containing mucus and carbonates but no ferments. The mucosa of the fundus secretes hydrochloric acid, pepsin, rennin and a small amount of lipase; like the pyloric and cardiac mucosa, it secretes mucus also. In addition to these external secretions, the stomach produces two principles of importance: (1) the pyloric mucosa produces a substance or hormone which by way of the blood stream stimulates secretion of hydrochloric acid; (2) part or all of the gastric mucosa produces an intrinsic factor (or its precursor) which prevents pernicious anemia

Innervation of Gastric Secretion.—The vagi are the main secretory nerves to the stomach. Section of the vagi prevents appetite secretion (cephalic phase). Stimulation of the peripheral ends of the cut vagi provokes secretion of gastric juice with high acid and pepsin values. Like gastric motility (*vide supra*), this reaction is produced most likely through liberation of acetylcholine at the intragastric endings of the vagus nerves. Injection of sufficient doses of acetylcholine or its esters (mecholyl, etc.) is accompanied by greatly increased secretion of fluid, acid and pepsin, especially when repeated injections are given.[175] Contrary results[159] probably were due to the swallowing of saliva, as my associates and I were able to demonstrate. Faroy and Deron[68] showed that repeated injections of acetylcholine restored the acid response in cases of anacidity. The effect of acetylcholine on gastric secretion is peciliar: after its repeated administration the gastric mucosa is temporarily refractory to histamine stimulation; conversely, mecholyl depresses gastric secretion provoked by histamine.[175] Alley[1] reported that histamine lowered gastric secretion to a meal and to sham feeding; this is in line with our observations. Atropine prevents acetylcholine from becoming effective (*vide supra*). It has been used more or less successfully in cases of hypersecretion with high acidity; rather large and repeated doses have to be given to attain satisfactory and constant depression of acidity. Histamine secretion is not much affected by atropine, which may even raise gastric acidity.[190] Stimulation of the splanchnic nerves and administration of epinephrine (by injection, *per os*, in the intestine or in a gastric pouch) provoke gastric secretion, although much less than stimulation of the vagi. Cutting of the vagi to the stomach, as performed when a Pavlov pouch is converted into a Heidenhain pouch, usually is followed by an abundant secretion of acid juice from the stimulated pouch, which subsides eventually; slowly, most Heidenhain pouches lose much of their secretory power, and their response to food and histamine drops to low values. Pavlov pouches, on the other hand, maintain a normal secretion indefinitely. There is little doubt that the absence of vagal innervation with the Heidenhain pouch must be held responsible for this phenomenon.

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* I have had good experience with "klim" in a great number of tests on emptying time in dogs.

Wolf and Wolff have made interesting observations on secretion in a subject with a large gastric fistula. They stated that "when a . . . large volume of gastric juice with high . . . acidity accumulates . . . the mucous membrane is relatively red and . . . no vigorous contractions are taking place. . . . When a small volume of gastric juice with high . . . acidity is obtained . . . the mucous membrane is . . . engorged . . . and . . . in addition, . . . vigorous contractions are taking place. Low acid volumes in the presence of small volumes of gastric juice . . . suggest that the . . . mucosa is . . . pale and . . . no vigorous contractions are taking place."[273]

Subtotal Gastrectomy.—Some surgeons have advocated section of the vagus nerves at the cardia to reduce acid secretion. This procedure eliminates psychic secretion and may diminish the volume but not the degree of acidity. In order to diminish acid secretion sufficiently, many surgeons resect 60 per cent and more of the stomach. Since this procedure does not reduce acid secretion of the gastric stump sufficiently in a number of patients, especially those with duodenal ulcer, some surgeons have added section of a number of branches of the vagus of the cardia, based in part on the observation that atropine is able to suppress acid secretion in patients who have undergone subtotal gastrectomy. In 26 of 34 patients this procedure produced permanent anacidity;[267] in the dog subtotal gastrectomy plus section of all vagus fibers at the cardia did not permanently reduce acid secretion of a pouch or of the main stomach.[227] Dragstedt and Owens[59] in 1943 resected all vagus fibers in the lower part of the chest in two patients suffering from chronic duodenal ulcer. Gastric acidity and volume of secretion during the night were reduced considerably; no swallowing difficulties were observed. Although the periods of observation were short (one and two months, respectively), these results may be of importance if no late complications or recovery of gastric secretion occurs.

Great puzzles to the surgeon and the physiologist are why patients with duodenal ulcer usually have high gastric acidity, while those with gastric ulcer usually have a normal or low value, and why operations for relief of gastric ulcer are more satisfactory than those for duodenal ulcer. Subtotal gastric resection is done with a low mortality rate now, and on the whole its results are satisfactory. The rationale for this may be found in some or all of the following facts: the ulcer-bearing area is excised; gastric emptying time is reduced, and duodenal regurgitation occurs freely; much of the acid-secretory area is resected and, even if the remaining fundus may secrete maximally, the total volume of acid is reduced and can be neutralized easier; gastritis, found in many gastric stumps so produced, may reduce acid secretion; the hormonal mechanism of the pyloric antrum has been eliminated. Yet a small percentage of patients are not cured and suffer from pains and discomfort similar to those before operation and from further ulcers in the stomach or anastomosed intestine.

Secretion of Hydrochloric Acid.—This is one of the body's most powerful mechanisms and cannot be fatigued except under extreme unphysiologic or pathologic conditions.[140] Continued complete loss of gastric secretion is fatal within a short time.[58] Gastrectomy in the growing monkey was found to impair intestinal digestion and absorption. Decreased serum calcium and generalized severe osteoporosis and fibrosis (one year later) indicated calcium deficiency. Increased size and histologic changes in the parathyroid gland indicated functional hyperactivity. Serum phosphatase was elevated.[75] Secretion of acid does not seem to be related to body build, position or emptying rate of the stomach (Lander *et al.*,[134] 1934; Vanzant *et al.*,[255] 1936). The total amount of gastric juice secreted by an adult man of average size in twenty-four hours has been estimated to vary between 2,000 and 3,000 cubic centimeters of fluid.[206] Variations in the osmotic pressure of the blood have been reported to be associated with parallel changes in osmotic pressure (*i. e.*, chlorine concentration) of the gastric juice.[80] A precursor of hydrochloric acid is produced by the parietal cells of the fundus from the chlorine of sodium chloride taken from the blood. This precursor, of unknown composition, gives off free hydrochloric acid in the lumen of the tubules of the glands (Davenport;[55] Gray;[87] Hollander[102]). The venous blood of the stomach is therefore more alkaline than its arterial blood, and at the height of a good normal secretion to a meal, especially to meat, the alkalinity of systemic venous blood is increased slightly but measurably. This change is indicated by a simultaneous rise of urinary alkalinity, the urinary "alkaline tide." Both reactions are of little clinical value as indicators of gastric function, for which they were proposed, because of their variability and inconsistency; this is due to the alkaline pancreatic secretion which follows and overlaps gastric secretion, to other regulatory mechanisms of blood *p*H, like the lungs, and to reabsorption of the gastric secretions in the intestine. In gastrectomized animals and man an "acid tide" of the urine appears, which is the expression of a postprandial acidosis. This is due to temporary loss by the blood of alkali secreted by the pancreas. This phenomenon is accompanied by increases of calcium and of phosphorus in the urine.[40]

After strenuous exercise during the interdigestive period, the alkalinity of the blood may be lowered by lactic acid; then an appetizing meal will quickly restore the average alkalinity of the blood, by withdrawing chlorine from it temporarily to form gastric hydrochloric acid. This effect has been described[117] as responsible for the refreshing effects of foods during extreme physical fatigue.

On the concentration of hydrochloric acid secreted by the parietal cell, two schools of thought have dominated the picture: (1) the older one, of Pavlov, according to whom hydrochloric acid is secreted at a constant concentration with the rate of secretion only depending on the intensity of the stimulus, and the rise of concentration at the beginning and its drop at the end of a period of secretion are due to dilution and neutralization of hydrochloric acid by the alkaline secretions of the mucous cells; (2) the second one, represented by Rosenmann, according to whom the concentration of hydrochloric acid secreted varies directly with the intensity of the secretory stimulus, and the total chlorine in the gastric juice is constant, but not its partitions of free hydrochloric acid and base. In the course of time the genius of Pavlov has prevailed, and recently Hollander,[101] Liu, Yuan and Lim[131] and Wang[260] have shown that gastric hydrochloric acid is secreted at a constant concentration of about 170 millimols (or clinical units)—*i. e.*, is isotonic with blood. Therefore, the lower values of acidity usually found in the normal stomach, free of regurgitation, are due mostly to its neutralizing and diluting secretions, which are more apparent naturally at the beginning and at the end of a secretory period, when smaller quantities of acid are secreted. Helmer[94] has found that mucous secretion is responsible for the main variations in gastric acidity in human beings, by neutralizing and diluting the parietal hydrochloric acid secretion. The ratio of 10.1 for sodium to phosphorus in the mucus compared to that of 0.62; 1 in saliva was used to estimate the contents of saliva in the gastric juice. Duodenal regurgitation is certainly a factor in the regulation of gastric acidity, but apparently not of such importance as assumed by Boldyreff.[31] It has been shown that saliva and hepatic bile have a slight secretagog effect on gastric acid secretion; bile and pancreatic juice stimulated mucous secretion slightly.[119] Experimental evidence has been brought forward of the existence of an intragastric regulatory mechanism for the degree of free acidity; *i. e.*, when gastric acidity reaches its upper limits, an inhibitory mechanism prevents further secretion of hydrochloric acid.[254] Another regulatory mechanism seems to be of great importance: hydrochloric acid in the duodenum lowers the gastric secretion of acid, inhibits gastric motility and relaxes the pyloric sphincter, thus permitting duodenal regurgitation (Thomas *et al.*;[242] Wilhelmj *et al.*[263]).

Clearly, one cannot speak about hypersecretion of hydrochloric acid. If a person had 170 millimols (or clinical units) of free or combined hydrochloric acid in his stomach juice, this would be his maximum physiologic secretory capacity. Actually, food, saliva, duodenal regurgitation and gastric mucous and alkaline secretion, as well as intragastric and enteral regulatory mechanisms, prevent gastric hydrochloric acid from being so high, either by dilution or by depression of secretion. It follows also that hypersecretion in volume but not in acidity can occur. High acid values in human gastric juice, therefore, should be called not hyperchlorhydria but a symptom of deficient neutralization or inhibition.

Effect of Foods on Gastric Secretion.—Meat and fish stimulate gastric secretion most; bread is next, and milk stimulates least of all. Addition of water to a meal raises gastric secretion. Vegetables and vegetable soups are good secretagogs. Of breakfast foods and drinks, those provoke most secretion that contain most roast products. Cocoa is most effective, coffee less and tea least. Toasted bread is a better secretagog than fresh bread (Kestner and Warburg;[118] Babkin;[13] Sehestedt[225]). Colloidal starch was found to depress peptic digestion. The amylopsin of saliva hydrolyzes starch and abolishes inhibition of pepsin (Maxwell;[149] Nakagawa[161]). Bolting of food or the depression of salivary secretion in the aged[157] may thus interfere with gastric digestion of proteins.

The existence of a gastric hormone, *gastrin,* was put forward by Edkins,[62] who demonstrated that injection into an animal of an acid extract of the pyloric mucosa was followed by secretion of acid by the fundus. He established the theory that once gastric secretion has begun it is augmented by the action of hydrochloric acid on the pyloric mucosa. Later it was shown that other animal or plant tissues yield substances similar to gastrin, and Schnedorf and Ivy[219] identified gastrin with histamine. Reports from Babkin's laboratory in 1938[127] and 1942[129] seemed to bring good evidence against gastrin being histamine. Necheles and Lim[169] and others have demonstrated the presence of substances which stimulate gastric secretion in the viviperfusate of the blood of fed dogs. The first experimental evidence of a humoral function of the pyloric mucosa dates from Pavlov's laboratory;[110] removal of a dog's pyloric antrum lowered gastric acid secretion following a meal, and food inserted into a pyloric pouch (but not into the main stomach) stimulated acid secretion of the stomach of the same dog. Portis and Portis[193] performed the Polya type of resection on dogs with Pavlov pouches. They found that the stimulated acid secretion of the pouch did not differ materially before and after resection of about 50 per cent of the total stomach. It would seem, therefore, that the pyloric antrum plays no role in acid secretion. The emptying time of the dog's stomach was shortened to half, however, after the operation, and I feel that whatever diminution of acid secretion occurred in these experiments by the lack of pyloric mucosa was made up by faster emptying and increased effects of the intestinal phase of gastric secretion, *i. e.,* by absorption of products of digestion, etc., from the small intestine. The same criticism must be applied to most similar work. A recent paper from Mann's laboratory[139] opened a new approach to the subject. Through an incision over the pyloric antrum the entire pyloric mucosa was excised and an anastomosis between the mucosa of the duodenum and that of the fundus established. By this method the muscular mechanism of the pylorus was left practically intact. The secretion of the stomach was diminished strikingly, except in some cases in which some pyloric mucosa was left behind. More work is necessary to clear up the problem, but I am of the opinion that the evidence at hand favors the concept of a humoral mechanism in the pyloric mucosa, whether by gastrin or by some other compound, which raises gastric acid secretion. With this point in mind, surgeons would act logically in excising the entire pyloric antrum with a large part of the fundus for the treatment of peptic ulcer; unfortunately, there are a number of other powerful factors present in many cases of ulcer which cannot be attacked surgically.

Gastric secretion is best divided into the basal, or interdigestive, the cephalic, the gastric and the intestinal phase.

Vitamins.—**A**: The free and total acidity and the rate of gastric secretion in response to histamine were not changed in dogs during avitaminosis A[99] or during total avitaminosis.[261] In response to administration of vitamin A, patients with anacidity or hypoacidity associated with gastritis were reported to have increased acid secretion, while patients with ulcer of the stomach or duodenum did not show consistent changes of gastric acidity, but were considered to have improved clinically (Boller;[32] Kluth;[125] Foldes and Vajda[71]).

B: Practically total B avitaminosis in dogs was followed by complete achlorhydria without anorexia or inanition. Administration of brewers' yeast restored normal gastric secretion within three days (Webster and Armour;[261] Babkin[17]). Administration of vitamin B_1 without B_2 likewise restored gastric secretion (Cowgill and Gillman;[53] Schiffrin and Ivy[214]). Vitamin B_1 fed to normal dogs was reported to stimulate the parietal cells and vagus endings and produce increased acid secretion,[77] but negative results also have been reported (Dyer and Roe;[61] Voit and Arnold[258]).

In man also, contradictory results have been obtained. Gottlebe[83] reported that acid secretion was increased after intravenous administration of crystalline vitamin B_1 to both normal and diabetic subjects (many persons with diabetes have hypo- or achlorhydria). Achlorhydria did not accompany beriberi and did not always exist with pellagra or with macrocystic anemia in alcoholic patients. This would suggest that the factor preventing pellagra (or black tongue) is not identical with the achlorhydria-preventing factor. An unknown fraction of the vitamin B complex has been held responsible for achlorhydria in a number of cases of pellagra and of macrocytic anemia (Cowgill and Gillman;[53] Joffe and Joliffe[115]). Alvarez and his associates[6] and Williams and his associates[266] induced vitamin B_1 deficiency, evidenced by anorexia and other deficiency symptoms, in normal subjects, without reduction in gastric acidity. Gastritis and pernicious anemia have been related to chronic deficiency of some member of the C complex[214] (see also "Intrinsic Factor," *infra*). In some cases, ventriculin administration ameliorated the symptoms of pellagra and increased gastric acid secretion,[142] while in others oral administration of hydrochloric acid was necessary to increase secretion. In normal persons, nicotinic acid had a histamine-like effect on gastric secretion, even when fasting anacidity was present, but the change was less than that produced by 1 mg. of histamine.[181]. In persons with achylia gastrica, no such effect was observed.[143]

C: The depression of gastric secretion in guinea-pigs with advanced scurvy has been attributed to secondary changes (Nordstrom;[182] Roe *et al.*[202]). Vitamin C has no effect on gastric secretion in human beings (Issler and Demole;[109] Boller;[32] Webster and Armour[261]). Café and Dulce[41] found that intravenous administration of ascorbic acid increased volume and free and total acidity; Lucksch[142] reported that the giving of vitamin C in addition to other measures improved gastric acid secretion in pellagra and other diseases characterized by hydrochloric acid deficiency.

D: The depression of gastric secretion following administration of vitamin D, apparently due to elevation in the level of calcium in the blood, is discussed under "Inhibition of Gastric Secretion" (*vide infra*). Kluth[125] and Webster and Armour[261] observed no effect of vitamin D on gastric secretion.

The Interdigestive, or Basal, Phase.—This should be defined as gastric secretion when the stomach and intestines are void of digestible or absorbable food. In relation to man the matter has been more controversial than in regard to animals, naturally.[111] Some authors reported that acid secretion practically ceased during sleep and suddenly appeared at awakening. Continuous secretion of acid, including nocturnal, was described by the same authors in patients with duodenal or gastric ulcer. Other authors reported higher secretion of acid at night than after a test meal. It is believed by some that nocturnal secretion of acid in normal persons depends on the diet of the subject; Babkin, for instance, expressed the belief that the rich American diet would hardly permit interdigestive gastric rest. I believe that the negative evidence carries more weight than the positive, and that an interdigestive phase with little or no acid secretion exists in many persons during sleep, but rarely during the day, and that its occurrence may depend on diet and the excitability of the gastric secretory mechanism. The contents of the stomach of a human being after awaking in the morning (residue) may be due (1) to some night secretion retained in the stomach or (2) to the sudden onset of secretion immediately after awaking, as described. The volume of such residue has been described as varying between a few and 180 cubic centimeters in normal persons (Boas;[30] Rehfuss and associates;[199] Fowler and associates;[73] Carlson[43]). Since thinking of food, swallowing of saliva and regurgitation of duodenal juices act as stimulants of gastric secretion, the question of complete gastric secretory rest in the daytime, at least in the human being, is rather an academic one. Most of the aforementioned factors play a role also in pouch dogs; even when such animals are starved for many days, their basal secretion may contain free acid. I have seen a number of such dogs, however, in which fluoroscopy revealed bones or hooves in the intestine which acted as stimulants to gastric secretion. In a great number of dogs under complete basal conditions, I have seen complete absence of any gastric secretion of acid, a few drops of mucoid, alkaline secretion being voided from the pouch per hour. This is in agreement with the observations of Pavlov.

The Cephalic Phase.—The cephalic phase (Lim) (psychic secretion) is gastric secretion stimulated by thinking of, or suggestion in hypnosis, by smelling, by tasting or by chewing only of palatable food and possibly also by dreaming of good food. Pavlov's conditioned reflex belongs in this group also (integrity of its cortical representation is necessary). The central stimulus is transmitted to the stomach by way of the vagus nerves and is completely abolished when they are sectioned. This secretion is not acquired but inherited.[49] While in dogs psychic factors are powerful stimulants of acid secretion, their role in man is controversial. Some authors have called psychic secretion the most powerful one (Wilhelmj and associates;[263] Carlson;[43] Rehfuss;[197] and others). In a series of tests the chewing of a chilled orange produced a medium increase of acidity in a group of normal persons and a somewhat larger (statistically significant) increase in a group of ulcer patients.[170]

The Gastric Phase.—This consists of a mechanical and a chemical factor. Distention of the stomach produces a slight acid secretion. A number of substances stimulate acid secretion locally in the stomach, acting through the humoral pyloric mechanism discussed previously.[14] Alcohol and histamine act on the glands directly; alcohol is also absorbed in the stomach, especially when the beverage is carbonated, and then reacts from the blood, stimulating the parietal cells again. Alcohol injected intravenously or given by rectum is partly excreted into the stomach and stimulates gastric secretion; this is believed to be due to liberation of histamine.[111] On continued administration alcohol may become a conditioned stimulus for gastric secretion and then produce not only acid but pepsin secretion. This may explain the otherwise not understood effect of stomachics (Carlson;[43] Krueger and McIntosh[131]). The application of procaine to the gastric mucosa abolishes the secretory response to distention and to local application of secretagogs. Ivy expressed the belief that a local mechanical and chemical receptor mechanism is blocked by the procaine.[111]

The Intestinal Phase.—The intestinal phase is due to the absorption of digestion products and possibly humoral substances from the small intestine during the process of intestinal digestion and absorption; these act from the blood on the secretory cells.[110] Absorption of histamine from the large intestine, where it may be formed from histidine by bacterial action, is questionable. Histamine is one of the strongest stimulants of gastric acid secretion; it acts directly on the parietal cells. The intestinal mucosa contains much histaminase, an enzyme which destroys histamine.

Constituents of Gastric Juice.—**Pepsin.**—Pepsin is secreted by the chief cells of the fundus. Inside the chief cells is its inactive precursor, pepsinogen, activated by hydrochloric acid in the stomach. Pepsin splits proteins into albumoses and peptones. Contact with gastric juice, even of short duration, enhances tryptic digestion of proteins.[176] The optimum *p*H for peptic digestion varies between 1.4 and 2.2, depending on the optimum ionization of the substrate and other factors.[183] In a more alkaline medium, above *p*H 4, pepsin rapidly loses its activity, especially at body temperature. Pepsin is destroyed at temperatures of 50 C. and above. It does not hydrolyze peptones, protamines and nucleotides.

Sham feeding, vagus stimulation, appetite and meal secretion and the administration of pilocarpine, of acetylcholine and its esters and of insulin but not of histamine provoke a secretion of gastric juice rich in pepsin (Toby;[244] Bowie and Vineberg;[35] Babkin;[13 14] Necheles *et al.*[175]). A number of other authors have stated that histamine increases pepsin secretion.

The question of digestion of proteins by patients with gastric anacidity or achylia is important. If these persons are careful with diet, chewing of food, asepsis, etc., they digest proteins as do normal persons. This is due to tryptic digestion in the stomach by regurgitated duodenal juices and subsequent digestion in the upper part of the small intestine.[100] These patients are prone to suffer from diarrhea, owing to fast gastric emptying and entrance of more or less undigested, infected food into the small intestine. Hydrochloric acid and pepsin mixtures given with meals will greatly benefit such përsons. Likewise, after total resection of the stomach, tryptic digestion will keep a person alive and will if the aforementioned precautions are adhered to. Gastric hydrochloric acid is not absolutely necessary for stimulation of pancreatic secretion. The pancreas has a psychic secretion and is stimulated by foods, especially fats, their breakdown products and those of the proteins, in the upper part of the small intestine.[188] Pepsin is destroyed *in vitro* by small quantities of detergents like sodium lauryl sulfate (Dreft). *In vivo,* in the dog and in the human being, the destruction of pepsin in the stomach was not or only incompletely attained (Kirsner;[121] Steigmann and Marks[237]). Schoch and Fogelson[221 222] used Dreft in the treatment of peptic ulcer in dogs and in human beings, in the belief that pepsin plays an important role in ulcer formation. I do not feel that this assumption is justified.[165] Aluminum hydroxide and phosphate inhibit peptic activity in gastric juice not only by lowering its acidity and inactivating or precipitating pepsin, but by the liberation of aluminum ions in acid juice (pH < 2) and by the formation of soluble compounds of aluminum hydroxide or phosphate. The latter form highly viscous precipitates with the mucoproteins of the gastric juice which are resistant to peptic digestion, and which presumably protect the gastric mucosa against peptic corrosion.[128]

Rennin.—Rennin is not identical with pepsin. Both rennin and pepsin clot milk; this is fortunate, because rennin is destroyed by pepsin. Rennin is absent in the adult's gastric juice;[57] it seems to play a role in digestion in the young infant, whose pepsin secretion may be deficient for the requirements of a pure milk diet. The clotting of the milk in the stomach is responsible for the retention of the milk in the stomach for several hours (whole milk; skimmed milk stays less time in the stomach). For two reasons this is of great importance, especially in children: (1) The retention of the coagulum in the stomach enhances its digestion and prevents absorption of unaltered casein from the intestine, with its possible allergic sequelae. (2) Fluids leave the stomach so fast that the bactericidal action of hydrochloric acid cannot take effect. Clotted milk stays in the stomach for a considerable period and can be sterilized there to a high degree. While the whey leaves the stomach rapidly, it is highly probable that the clotted milk (paracasein) contains most bacteria by coprecipitation and absorption. The clotted milk contains practically all the milk fat. In the infant gastric lipase seems to be of greater importance than in the adult, and a certain degree of fat digestion occurs in its stomach. Since rennin needs calcium to induce clotting, it is a pernicious principle to add to the milk drugs which precipitate calcium. This is done during the hot season in order to prevent clotting. Summer diarrhea of children may be explained by such practices.

Lipase.—Lipase is secreted in minute amounts and has hardly any significance in gastric digestion in the adult.

Urease.—Urease occurs in normal gastric juice; its presence may explain the relatively large amount of ammonia and the small amount of urea found in a normal specimen of gastric secretion.[135]

Mucus.—Mucus is secreted by the epithelium of the entire surface of the stomach, by the mucoid neck cells of the fundus and by the cardiac and pyloric gland cells. Little is known about the regulation of its secretion (Babkin;[13] Vineberg;[257] Jennings and Florey[114]). It seems that the resting stomach secretes mucus; that during active secretion of hydrochloric acid, mucus secretion is decreased, to practical absence at the peak of acid secretion (especially following histamine), and that gradual return of mucus secretion accompanies dropping acid secretion—in other words, an apparent inverse relation exists. ?While noxious agents (acids, silver nitrate, etc.) and drugs (pilocarpine) raise mucus secretion, no normal mechanism is known to do so. In animal experiments, stimulation of the vagi has produced some, and of the sympathetic nerves, a larger, amount of gastric mucus. Section of both splanchnic nerves in the cat produces a "paralytic" secretion of mucus. Injection of epinephrine is followed by secretion of mucus. Administration of atropine does not abolish this adrenosympathetic mucus secretion, the greatest part of which is obtained from the pyloric antrum.[15] The pyloric mucosa secretes, besides mucus, an alkaline diluting fluid containing chiefly bicarbonate and neutral chloride. The main purpose attributed to gastric mucus is its protective action on the gastric mucosa. This is believed to be twofold: (1) mechanical, *i. e.*, by making foods slippery or by preventing gastric hydrochloric acid from acting directly on the surface mucosa; (2) chemical, by neutralizing the hydrochloric acid. Since topically hydrochloric acid is secreted below the mucus-secreting area, it is doubtful whether mucus can protect the gastric mucosa from contact with acid. Besides, at the height of acid secretion, when most protection should be needed, little mucus is produced, and when acid secretion drops to low values, the amount of mucus in the gastric juice rises. The question of the role of mucus or of its breakdown products (chrondroitin salts) in the protection of the gastric mucosa has been raised again recently by Komarov[128] and by Wolf and Wolff.[271b].

Apparently two kinds of mucus are secreted, soluble and visible; the first supposedly from the mucous neck cells in the fundic, pyloric and cardiac glands and the second from the glands of the surface epithelium. Both are mucoproteids, and the characteristic difference between them seems to consist in their contents of dextrose. Mucus contains chrondroitin, a compound whose physiologic function is little understood, but which may play a role in gastric secretion and liver function. Chrondroitin has been found to prevent the formation of erosions in the gizzard of the chick,[3] and it has been claimed to be beneficial in cases of migraine. Visible mucus is dissolved and partly digested by gastric juice and certainly is a factor in the neutralization of small amounts of hydrochloric acid secreted. Soluble and visible mucus have been reported diminished in cases of peptic ulcer (Necheles and Coyne;[167] Anderson *et al.*[8]).

It has been reported that the mucosa of the stomach and duodenum is more resistant to corrosion by hydrochloric acid under certain experimental conditions, *i. e.*, when the animal has been fed prior to the test (the food having left the stomach already) or when the gastroduodenal mucosa has been irrigated with peptone solution.

A commercial preparation of hog's mucin has been used as an antacid in the treatment of peptic ulcer.[70] While the acid-binding capacity of this preparation is considerable, it is not true gastric mucin, but the product of acid-pepsin digestion of mucus and scraped-off mucosa of hog's stomach, to which, besides, a certain amount of alkali and peptones has been added. It is well possible that hog's mucin may have a protective effect similar to that described by Langenskiold,[135] especially because it contains peptones (*vide supra*). We[166] have found that mucilaginous substances (hog's mucin, okra and agar) shorten the emptying time of the stomach.

Intrinsic Factor.—Stomach juice and gastric mucosa contain an unknown substance which reacts with the proteins of the food to form the intrinsic factor (or a close precursor) which is essential for blood formation and in the absence or decreased production of which pernicious anemia will develop. In pernicious anemia there is gastritis of one form or another.[28] and hydrochloric acid, pepsin and rennin are absent in almost every case; therefore, the production of the intrinsic factor has been associated with the fundic area. Recently Meulengracht[151] has shown that in the pig the intrinsic factor is present in the duodenum, the pyloric antrum and a small area of cardiac mucosa ("pyloric gland organ"), and he assumed the same for man. Lately, however, he reported[152] that histologic study of autopsy material in cases of pernicious anemia revealed that, while the fundic area was atrophic, the "pyloric gland organ" was normal. Total resection of the stomach in man is not followed by pernicious anemia (a few exceptions are probably insignificant), and it has been shown in the pig, for instance, that the duodenum[243] and colon[210] also contain the intrinsic factor. In the dog, resection of three-fourths of the stomach, the entire duodenum and the upper part of the jejunum is not followed by pernicious anemia.[18] In patients with pernicious anemia, the volume of gastric secretion is diminished to a fraction of normal, and although it still contains some of the intrinsic factor, this seems to be deficient in quantity.[108] It is an open question whether Castle's intrinsic factor, hemopoietin[265] is identical with another factor (P. neuropoietin[106].) which maintains a normal state of the skin and central nervous system. In gastrectomized man and young pigs a condition similar to pellagra may develop.[189] I feel that pernicious anemia is due primarily not to existing gastritis but to the prolonged lack of a factor unknown as yet, possibly a vitamin, in the absence of which degenerative changes occur in the nervous system or in the stomach and other organs, or in all of them in turn; the gastric mucosa is thus predisposed to secondary gastritis. Schindler and Serby[218] expressed this ably in their paper:

> It is almost unbelievable that an inflammatory process of unknown origin should destroy the gastric mucosa to such an extent as to prevent the formation of a hormone and that this same inflammatory process should be healed by administration of exactly the same hormone.

Other Constituents of Gastric Juice.—Practically all constituents of the blood seems to occur in gastric juice; many of them, of course, modified by enzymatic action. The normal stomach contains mucoproteids, which are increased in amount in superficial and hypertrophic gastritis and in gastric cancer. This increase has been recommended for diagnostic purposes.[96] Normal gastric juice contains nonprotein nitrogen, 25.35 mg., uric acid, 2 to 5 mg., ammonia, 5 to 7 mg., urea, 2 to 4 mg., and aminoacids, 5.7 mg. per hundred cubic centimeters. In benign achlorhydria these constituents occur in about double concentrations; in pernicious anemia, in triple, and in gastric carcinoma with achlorhydria, in quadruple. This last finding may be of significance in the differential diagnosis between gastric ulcer and carcinoma. In cases of increased nonprotein nitrogen in the blood, higher concentrations of the various nonprotein nitrogen fractions can be found in gastric juice (Martin, 1931,[144] 1933,[145] 1938,[147] Carlson, [43] 1916, and others). The secretion of the normal resting stomach contains occasional leukocytes, which increase in number during digestion (digestive leukopedesis). In certain conditions of allergy, the gastric contents have been described as containing many eosinophils.

Calcium.—The concentration of calcium in gastric juice is inversely related to the acidity. It has been considered to be part of the nonparietal (diluting) secretion of the stomach (Val Dez;[249] Grant[85]), most of it occurring apparently in the gastriē mucus.[85]

Bromine.—Bromine has long been known to be capable of taking the place of chlorine in stomach juice if the chlorine in the food is replaced by bromine. Chatagnon[48] has found small amounts of hydrobromic acid in normal gastric secretion. After medication with bromine salts he noticed that bromine was retained and eliminated slowly by the stomach. This may be kept in mind in the administration of bromine salts to patients with irritable stomach.

Lactic Acid.—Lactic acid is not secreted by the stomach, but is the product of bacterial decomposition of carbohydrates in cases of gastric retention and in a few cases of atrophic gastritis.[216] It is also found in cases of decaying carcinoma of the stomach, when its presence may be due to diffusion from the cancer cells, which produce it abundantly in their carbohydrate catabolism, and to bacterial action. Therefore, lactic acid and lactic acid bacilli are not necessarily indicative of gastric cancer, but may indicate retention or possibly atrophic gastritis. Production of lactic acid by bacteria proceeds in a slightly acid or neutral environment. In achlorhydric stomachs without retention and with nonulcerating carcinoma, usually no lactic acid is found. This is probably due to the periodic washing out of the stomach by liquids, etc., and the lack of retention of food.

Potassium Thiocyanate.—Potassium thiocyanate is found in human gastric juice and is believed to be excreted by the stomach rather than derived only from swallowed saliva;[180] nothing is known about its functions.

About *other rare substances* and poisons excreted into the stomach, see Rosemann.[204]

Other Functions of Gastric Secretion.—In most cases of microcytic anemia the secretion of hydrochloric acid is diminished or absent. A common cause may produce both the diminution of gastric hydrochloric acid and the anemia. On the other hand, we[239] found total and even subtotal gastric resection in man frequently (but not always) followed by microcytic anemia, which is increased when the organism loses more iron, as in pregnancy. One of the functions of gastric hydrochloric acid is to bring into solution, and thereby utilize, the iron contained in the food, facilitating its absorption in the intestine. It has been shown that, within certain limits, a relation exists between the degree of gastric acidity and the hemoglobin concentration in the blood (Lerman and associates;[138] Apperly and Cary[11]).

Acetylcholine[28] and *histamine*[15] have been found in gastric juice. Babkin[15] stated that he was inclined to attribute to histamine a role in the formation of gastric hydrochloric acid as well as of peptic ulcer.

Gastric hydrochloric acid plays a role also in the utilization of the *calcium* and *phosphorus* of the food. In young gastrectomized dogs on adequate diet severe rickets develops.[40]

Bactericidal Barrier of Normal Stomach.—The normal stomach and duodenum offer an effective protection against swallowed bacteria by acid and by bacteriophages or trypsin, respectively.[33] The question whether the bactericidal quality of gastric juice is dependent on factors other than hydrochloric acid is moot, but cannot be discarded lightly, in view of the bactericidal properties of saliva, prostatic secretion, colon contents, etc. (Hood;[104] Sebastianelli[224]). Gastric juice of pH 1 was found to be sterile between *p*H 1 and 2, it yielded occasional colonies; *p*H 3 was designated the borderline of bacterial growth, and above *p*H 3 heavy bacterial growth was found. The average time of disappearance of test organisms from the stomach was found to be one hour and eighteen minutes.[105] This demonstrates that even gastric juice of low acidity will offer a certain degree of protection. In stomachs with achlorhydria or achylia abundant growth of bacteria is found;[198] the same is true for most stomachs after gastroenterostomy or subtotal resection, although a number of such stomachs still are able to secrete acid. Ingestion of dilute hydrochloric or organic acid was found to decrease the viable gastric bacterial flora.[105] This may explain in part the beneficial effects of medication with dilute hydrochloric acid in cases of anacidity, gastroenterostomy or subtotal gastric resection (Necheles[165]). The aforementioned considerations demonstrate the value of a good secretion of hydrochloric acid; an important factor in this is psychic stimulation, depending on appetizing food and regular eating habits; the taking of fruit before meals, proposed by Bergeim and his associates,[24] and of tonics, apéritifs, appetizers, cocktails, etc., may be considered here.

Since fluids when taken alone leave the stomach rapidly, the relative sterility of these is of great importance, particularly in infants and in patients with fast gastric emptying time, often seen after certain operations (*vide supra*, under "Rennin").

The bacterial contents of the duodenum and biliary tract seem to depend largely on normal gastric acidity and function.[248]

Standards of Gastric Secretion.—In infants, acid and volume secretion are relatively low. With advancing years, acidity and volume diminish in the man, but less in the woman.[101] The greatest mass of statistical material on normal gastric secretion following a test meal is from the group of workers in the Mayo Clinic.[256] In 3,746 cases they found a steady increase in the incidence of achlorhydria from youth to old age. At the age of sixty years, 28 women in 100 failed to show free acid on repeated fractional analysis, and similarly, 23 men in 100 were achlorhydric. Free gastric acidity appears to rise rapidly from childhood up to the age of twenty, when adult values are reached. About the age of puberty the average value for body begins to rise considerably above that of girls. Throughout adult life the typical free acidity in women is 35 units; in man, 50 units for ages twenty to forty years. After the age of fifty years free acidity in man falls off gradually until the age of sixty-five, when it is the same as that of women. Combined acidity appears to remain practically constant throughout life, with no sex difference. This latter observation by the Mayo group may give the clue to the cause of the sex difference observed. The stomach seems to secrete a constant amount of hydrochloric acid at all ages, but the degree of neutralization varies with age; the most plausible explanation lies in the production of soluble mucus, which probably increases with the higher incidence of gastric disturbances, gastritis, etc., which accompany increasing years, and which presumably are greater in the male than in the female sex. Next to the skin, the mucosa of the stomach seems to me to be the most punished organ of the body.

Acidity is diminished in persons whose *physical condition* is poor, but the volume is little affected.[29] It is diminished also with fever or an artificial increase of body temperature.[88] Radiation of the stomach with

x-rays has been employed in order to depress gastric acid secretion. While this result occurs, it is doubtful whether it is due to local effects on the stomach only (Portis and Arens;[192] Snell and Bollman[234]).

Rubbing or cooling of the skin has been shown to be accompanied often by increased gastric secretion, due probably to histamine liberated from the skin. In acute skin diseases increased gastric acidity and in chronic ones decreased acidity have been described (Brown and associates;[38] Voss,[259] and others). Acidity and pepsin content seem to be relatively high in *high-strung persons* (Sagal *et al.*;[207] Alvarez *et al.*,[7] and others), a fact which should be a warning not to perform gastroenterostomy or a similar operation on such persons and even to think twice before performing subtotal gastric resection.

A constitutional factor in the degree of acidity may be seen in the following observation: we[158] have found healthy relatives of ulcer patients to have a (statistically significant) lower secretion of acid after a test meal than a comparable group of normal population without ulcer disease in the immediate family. Achlorhydria and "hyperacidity" seem to be hereditary (Apperly and Norris;[12] Apperly[10]).

Rehfuss and associates (1914) described three types of normal stomach on the basis of secretory activity: the isosecretory, the hyposecretory and the hypersecretory (continued secretion).

Inhibition of Gastric Secretion.—Oils, fat and dextrose (the last in high concentration) inhibit the secretion of hydrochloric acid and pepsin. While a neural mechanism may play a small role, a humoral agent described by Lim and his associates seems to explain the phenomenon. Oils and fat inhibit when they enter the small intestine, apparently owing to liberation into the blood stream of enterogastrone, as Lim named the inhibitory principle. Enterogastrone is contained in the mucosa of the small intestine, in the blood after feeding and in small concentrations in a number of other organs.[130] Recently I have found a similar substance in large amounts in the urine of normal human beings. Such substances may be of importance in the regulation of gastric acid and pepsin secretion and of emptying time and in the treatment of gastroduodenal ulcer (Necheles[165]). Evidently this is another regulating factor of humoral nature for gastric activity.[162–4] Recently, Brunschwig *et al.*[39] have extracted an inhibitory substance from the stomachs of normal persons and of patients with various diseases. This substance does not seem to be identical with enterogastrone and the urinary inhibiting principle, and its biologic role remains to be seen. Interestingly, fats inhibit gastric secretion and motility only for several hours (the period depends on the nature of the fat: the less its saturation the greater its inhibitory effect). After this primary period a more or less intense stimulation of gastric secretion occurs, which may reach such levels that the beneficial effect desired—in ulcer patients, for instance—is just reversed (Babkin;[13,14] Shay *et al.*;[229] Alley *et al.*[2]). Heartburn, which many persons experience soon after the ingestion of a fatty food, may be due to a prolonged stay of the food in the stomach and the subsequent entrance of bile into the stomach, some of it possibly entering the esophagus. The late heartburn following a fatty meal probably is due to the secondary acid secretion of the stomach, described previously. The prolonged stay of a fatty meal in the stomach is due not to closure of the pylorus but to relaxation of the stomach. The prevention, or rather delay, of inebriation by the drinking of olive oil prior to alcoholic indulgence is an age-old trick which is explained by the long delay in gastric emptying and the resulting delay in the rapid absorption of the alcohol in the small intestine. Oil of peppermint depresses gastric secretion and hastens emptying of the stomach (Strauss *et al.*;[239] Meyer *et al.*[153]). Gentle exercise before or after a test meal augments gastric acidity. Gastric secretion, motility and digestion are depressed by severe exercise, especially when the exercise is accompanied by emotional excitement. After a person has become conditioned to severe exercise, gastric functions do not seem to be disturbed much (Crandall:[54] Hellebrandt *et al.*[90,92,93]).

The effect of x-rays on gastric secretion in the dog and in man are variable and unpredictable. Depression of secretion lasting from a few days to many months was obtained in most subjects, while in others no change occurred. In some dogs, increased acid secretion preceded the depression. These experiments are definitely dangerous, because the liver and the intestines seem to be more sensitive than the stomach to the *x*-ray (Ivy *et al.*:[113] Palmer and Templeton[187]).

Hypercalcemia produced by parathormone or by vitamin D (activated ergosterol) depressed gastric acid and fluid secretion and increased pepsin secretion. This inhibition persisted after the serum calcium level had returned to normal. The effects of parathormone and of ergosterol on acid and fluid secretion were reversed in animals with Heidenhain (nonvagal) pouches and those who had undergone thyroparathyroidectomy (Babkin;[16] Schiffrin[213]). Carlson has reported that the emptying of the stomach was delayed after parathyroidectomy.[44] Hypocalcemia depresses gastric secretion.[212] Hypercalcemia following injection of calcium salts likewise depresses gastric secretion.[84]

In tropical climates, gastric secretion and motility have been found depressed. Curry, paprika and onions were found to counteract these disturbances (Borchardt;[34] Kestner[116]).

ABSORPTION IN THE STOMACH

The normal stomach is not an absorbing organ, and of the usual foods little or nothing passes its walls into the blood or the lymph stream. Some water and alcohol are absorbed. If alcohol is taken with carbonated beverages, or as sparkling wine or champagne, gastric absorption is faster. This may account for the fact that these beverages are more intoxicating; habitués, therefore, either replace soda with ice water or stir their beverage until most of the carbon dioxide is gone. Recent work on the dog has shown that the pyloric antrum may be responsible for most of the absorption occurring in the stomach.[50,51] Salicylate compounds are readily absorbed from the stomach, and absorption is faster with increasing acidity of the gastric juice. Sodium bicarbonate and magnesium oxide, which lower gastric acieity, diminish gastric absorption of acetylsalicylic acid. Salicylic acid is absorbed faster than the larger molecules of acetylsalicylic acid and other salicylate compounds.[36]

Poisons like strychnine, potassium cyanide, etc., are absorbed readily in the stomach. The latter poison acts after in the presence of free gastric hydrochloric acid, which liberates hydrocyanic acid. Strychnine, nicotine, cocaine, atropine and eserine are absorbed much faster when the gastric contents are alkaline.[245]

Phenolphthalein in alcoholic solution has been assumed to pass into the blood stream through defects in the gastric or duodenal mucosa and was then detected in the urine. This observation is the basis of a test proposed recently for the detection of gastrointestinal ulcers.[158] This and similar tests were not found to be reliable (Goldstein and Erber;[82] Steigmann and Dyniewicz;[236] Notkin *et al.*;[185] Slutzky and Wilhelmj[233]).

Little oxygen is absorbed in the stomach. Gases in the stomach are in equilibrium with the blood.

EXCRETION INTO THE STOMACH

Excretion of alcohol (after intravenous or rectal administration) has been described. A number of *dyes* are excreted by the gastric mucosa.[96] One of them, *neutral red*, has been used for testing gastric function (chromoscopic test). Its excretion seems to parallel the secretion of acid and to occur through the parietal cells. The concentration of neutral red in the gastric juice is not as closely correlated to the degree of stimulation as is the acid secretion of the stomach. With so-called hyperacidity its appearance in the stomach is hastened.[268] In pernicious anemia with complete achlorhydria no neutral red is excreted. If elimination of the dye by a diseased kidney is diminished, a compensatory gastric elimination independent of gastric acid secretion occurs. In gastritis with normal acidity the appearance of neutral red in the gastric juice is retarded; this seems to depend on the quantity of gastric mucus present.[89] Cases have been reported in which a histamine test did not show hydrochloric acid but in which neutral red was excreted, and *vice versa.* In order to make the dye excretion test more reliable, histamine has to be injected simultaneously. On the whole, it seems that a good fractional histamine test yields all the information which an additional dye test can give. In cases of nephritis, etc., with increased nonprotein nitrogen in the blood, the test substances are excreted into the stomach, which, like the intestines, may be considered an organ of vicarious excretion in cases of deficient renal function (*vide supra,* under "Other Constituents of Gastric Juice"). Morphine was not excreted into the stomach of dogs, whether habituated to the drug or not.[64] Sulfonamides are excreted in rather large amounts into the stomach. This may account for the nausea following in some cases even the parenteral administration of these drugs.[47]

TESTS FOR SECRETORY FUNCTION OF STOMACH

In persons studied over a long period, daily variations in the concentration of acid and of pepsin in the gastric juice were so marked that one gastric analysis or even three or four on successive days would have given a decidedly misleading idea of the usual ability of the particular stomach to secrete acid and pepsin. Possibly the greatest degree of variability is to be found in nervous persons, who react too much to their environment (Engelbach and Brown;[65] Alvarez and associates[7]). Klein[124] and others have shown that the Ewald test may show absence of free hydrochloric acid, whereas a Rehfuss test, when extended for more than two hours, may yield a moderate or considerable amount. The value of the Ewald meal has been somewhat over-estimated. The presence of free acid does not exclude carcinoma of the stomach, and its absence does not always indicate an existing malignant growth. Normally, anacidity is found in a percentage of young, otherwise healthy persons, the percentage increasing considerably with age (*vide supra*). The presence of lactic acid indicates a decaying carcinoma, retention or hypertrophic gastritis. High free acid in the secretion during fasting as well as after the Ewald meal is considered to indicate the presence of a duodenal ulcer; low acidity, that of gastric ulcer. However, a diagnosis cannot be based on these findings only, because there are too many exceptions to this rule. Duodenal ulcer may heal with high and relapse with low acid values.

With the Ewald meal it is proposed that the technic used by the Mayo Clinic group (*vide supra*) be employed, because only when standard methods are used by a great many clinicians will one be able eventually to compare results in different parts of the country and of the world. When the Ewald test yields no free and only a few units of combined acid, a histamine test should be performed; this can be done conveniently after the Ewald test (the stomach contents should be aspirated before the giving of the histamone). The usual dose of 0.1 mg. of histamine per 10 Kg. of body weight seems to be too high. I have had good experience with a dose of 0.35 mg. of histamine acid phosphate for persons of an average weight of 125 pounds (45.5 Kg.). The height of secretion occurs thirty to forty-five minutes after injection. Concerning the preparation of histamine used, one must keep in mind that the active part of any of its compounds is only the histamine base, and that the larger molecule of histamine acid phosphate,* for example, contains one-third only of the active base of histamine hydrochloride.[226] In the doses used histamine is effective only when given subcutaneously, and considering the shock it may produce when administered intravenously, one must ascertain before injection that the needle is not in a vein. Cases have been reported in which the Ewald meal, orange juice or beef broth produced free acidity, while histamine did not. In a number of cases observed over prolonged periods, histamine secretion was highly variable and periods of complete anacidity occurred (Schiff;[211] Palmer *et al.*([86]). Thus, although histamine is considered to be the most potent stimulant of the parietal cell (acid secretion), biologic or pathologic variations in the histamine response are possible. Occasionally, no gastric juice can be aspirated from the stomach tube, or bile and alkaline fluid are obtained. In the first case, the tube may be above or just below the cardia, or may be in a pocket of gastric mucosa. In the second, the tube may have slipped into the duodenum. Pushing down or partial withdrawal of the tube and having the sitting patient lean forward or bend to his right or left side may produce the desired result. The test meal (hypertonic) proposed by Wilhelmj and his associates[264] is too complicated for routine clinical use; the procedure was found to yield too high values for acidity at times, apparently owing to absorption of water in the stomach. Hollander and Glickstein[103] with Bandes[19] devised an isotonic test meal therefor. Stomach juice should be titrated immediately after aspiration and not left standing, even in the icebox, because in the presence of mucus rather rapid loss of acidity takes place; this can be observed when samples are left standing after the addition of Toepfer's reagent. For the same reason, stomach contents should not be filtered slowly, but the supernatant fluid aspirated in a pipet. In titrating gastric juice with sodium hydroxide

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* Ergamine acid phosphate.

(tenth-normal for clinical purposes) and dimethylaminoazobenzene (Toepfer's reagent), it is important to follow Michaelis' instructions to stop at the appearance of the salmon-red color. If one titrates to the lemon-yellow end-point, one measures not only the free hydrochloric acid but the acid combined with the gastric proteins (protein chlorides and phosphates) and the free phosphoric acid.[146] Titration to the end-point of the phenolphthalein indicator gives information on the buffer capacity of the gastric juice. In many patients who have had subtotal gastrectomy, gastric emptying is so rapid and duodenal or jejunal regurgitation so plentiful that occasional samples taken during an Ewald or a histamine test usually yield no free and little combined acid. Constant suction can overcome this, and we[179] have designed a convenient apparatus for this purpose.

INTRAGASTRIC TEMPERATURE

Intragastric temperature varies between 96.5 and 102.2 F., with an average of 99.3 F. Ingestion of cold foods, of ice water (250 cubic centimeters) or of icecream (90 Gm.) produced a marked decrease in gastric temperature, with an average recovery time of more than half an hour. The taking of ice water delayed gastric emptying. Drinking of coffee raised intragastric temperature considerably. On the other hand, no change of intragastric temperature was found after application over the stomach for an hour and longer of an ice bag, a hot water bag, an electric pad, an infra-red lamp, a diatherm or a hot wet pack.[97] The implications of these observations are of great interest, for the following reasons: Cold and heat do not penetrate through the abdominal wall to the stomach for the obvious reason that they are dissipated by the blood. One might have expected that the stomach, with its extremely efficient and abundant blood supply and its location in the splanchnic blood basin, would be able to dissipate heat or cold brought into it (and Hepburn did not use large amounts) very rapidly. Failure to do so raises the question whether such stimuli produce a vasomotor disturbance in the stomach, *i. e.*, diminish the rate of blood flow through it, and brings back to mind the old belief that gastric ulcer may be produced by ingestion of too hot or too cold foods. Since recently more and more evidence has been presented in support of the theory that the genesis of peptic ulcer is based on vasoconstriction,[162]. the foregoing ideas may be worth consideration. The ineffectiveness of external physical means in raising intragastric temperature need not mean that they are useless. They may well be effective through reflexes from the skin, in releasing spasm of the gastric musculature, etc.

EFFECTS OF EMOTIONS ON THE STOMACH

Concerning the effects of emotions on the stomach, the reader is referred to the monograph of Wittkower[269] and to the book of Dunbar.[60]

Gastric Secretion.—In 1834 Beaumont (1929 edition[22]) wrote:

> In fear and anger or whatever depresses or disturbs the nervous system—the villous coat becomes somtimes red and dry, and at other times, pale and moist, and loses its smooth and healthy appearance; the secretions become vitiated, greatly diminished, or entirely suppressed; the mucous coat scarcely perceptible; the follicles flat and flaccid, with secretion insufficient to protect the vascular and nervous papillae from irritation. There are sometimes found, on the internal coat of the stomach, eruptions, or deep red pimples.

These observations have been confirmed and amplified since then. Wittkower,[269] working with persons in the waking state and under hypnosis, found that emotions like fear, disgust, sadness, anger and joy do not depress secretion uniformly in all subjects, as previous authors had reported, but depress it in some subjects and increase it in others. Two of his experiments are noteworthy: two subjects with normal acidity and a normal response of acid secretion to an injection of histamine responded with complete suppression of the histamine response to unpleasant emotions; this effect was removed by suggestion of a happy situation (Wittkower,[269] p. 569). The author concluded that the possibility of psychogenic histamine-refractory achylia seems plausible. The quantity of juice found in the stomach was increased considerably under emotional influence in most of his subjects, while in a few, complete cessation of secretion occurred. The same emotions do not effect similar results in different persons, but each person seems to have his peculiar pattern of response, *i. e.*, hyperacid or hypoacid. No correlation could be found between the gastric secretory response and the vagotonic and sympathicotonic types of Eppinger and Hess.

The recent work of Wolf and Wolff[271, 272] with Richards[201] on a patient with a large gastric fistula is of particular interest. Fear and sadness were accompanied by blanching of the gastric mucosa and inhibition of secretion and motility. Anxiety, hostility and resentment elicited increased acid secretion, hypermotility, hyperemia and engorgement of the gastric mucosa resembling hypertrophic gastritis, associated with complaints about heartburn and abdominal pain; when the last described condition was sustained, mucosal erosions and hemorrhages were easily induced either spontaneously by vigorous gastric contractions, or by the most trifling traumas. Contact of acid with such an erosion was followed by increased acid secretion, further engorgement of the mucosa and, eventually, formation of an ulcer.

Gastric Motility.—It is known that gastric tonus and peristalsis in the same person are subject to considerable variations, especially in a nervous person. Dislike of the barium meal or apprehension during an *x*-ray examination may inhibit gastric motility, relax the stomach and close the pylorus. There is a relation between appetite and gastric tonus. The showing of a savory dish improved gastric tonus.[20] In disgust or fright or before fainting, the lower gastric pole was observed to sink considerably;[20] on the other hand, suggestion of disappearance of the patient's complaints led to the disappearance of previously existing gastroptosis, which increased again on suggestion of aggravation (Wittkower,[269] pp. 576, 591). Using the mucosal pattern of the stomach as an indication of its tonic condition, Wittkower observed in 5 of 8 persons a distinct intensification of gastric tonus on suggestion of emotions in hypnosis. He expressed the belief that the muscularis mucosae is not involved in this phenomenon, which is debatable. In some of his cases, emotions produced an *x*-ray pattern of the gastric mucosa which could have been interpreted as that of gastritis (p. 577). Scantlebury[209] recorded human gastric motility in hypnotized subjects. During light hypnosis, the suggestion of eating a hypothetical meal inhibited hunger contractions for a short time. Suggestion of hunger did not produce hunger motility. Dreaming occurred only in periods of active gastric peristalsis. Dreams, spontaneous or hypnotically induced, caused inhibition of gastric motility.

Gastric Neuroses.—Alexander has covered this subject in another chapter.

WHY DOES THE STOMACH NOT DIGEST ITSELF?

The normal gastric mucosa is not attacked in the least by the normal stomach juice; only when its blood supply is diminished will corrosion, digestion and a reactive gastritis occur.[217] Alternating exposure to duodenal and gastric juices may greatly enhance such processes[176] and may explain the preponderance of duodenal over gastric ulcer. Among the many theories trying to explain the resistance of living tissues of the stomach and intestine against digestion, the following one seems to be sufficient: their native proteins and lipoids resist digestion to a high degree, and the constant flow of alkaline blood and lymph through them prevents the action of hydrochloric acid and pepsin on the stomach and duodenum. Similarly, resistance to tryptic digestion (*e. g.*, in the achlorhydric stomach or during regurgitation) is prevented by tissue resistance and impermeability and the diluting effects of blood and lymph.[26]

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CHAPTER VII

CLINICAL ASPECTS OF GASTRIC SECRETION

THE physician is concerned with gastric secretion from two standpoints: (1) for purely biologic and physiologic considerations, of great interest but not necessarily of immediate clinical utility; (2) for practical conclusions with reference to diagnosis and treatment. It is with the second aspect that the present chapter is concerned.

In the early days of the study, standards of gastric secretion were set up, and it was believed that even moderate deviations from them indicated disease. A good deal of attention was paid to so-called hyperacidity and to subacidity, and absence of acid in the gastric secretions was believed to mean cancer or at least serious gastritis. Modern studies have greatly modified these conceptions, and it may be said in advance that measurement of the stomach secretions furnishes really useful information in only limited groups of cases. The main reason is not far to seek: the variations both in acidity and in volume of gastric secretion are so great in normal persons that few conclusions can be drawn in relation to disease. Thus, if one introduces a tube into the stomach under basal conditions and withdraws the gastric juice over a period without the use of any test meal or special stimulus, the acidity will be found to vary in different subjects from 0 to 120 degrees by the usual titration with dimethylaminoazobenzol and phenolphthalein.[8] The volume of secretion produced in ten minutes may be only a few drops or it may be as much as 20 to 30 cubic centimeters. After an injection of histamine—the most powerful known stimulant for gastric secretion—the acidity still varies greatly: although most normal subjects show values from 90 to 120, levels all the way from 0 to 160 may be encountered, and ten minute volume of secretion varies from 5 to 60 cubic centimeters.[9]

TESTS OF GASTRIC SECRETION

It is customary in clinical work to give some sort of "test meal" with the idea of stimulating gastric secretion. There are, however, many objections to such a procedure.[11] Briefly, the test meal dilutes the gastric juice to a variable degree; it also exercises a buffer effect, which obscures the true state of affairs. Furthermore, instead of relatively pure gastric secretion, a mixture of juice with a variable amount of foreign material is obtained for examination. Finally, the ordinary test meals do not furnish a stimulus sufficiently powerful to bring out the full capabilities of the secretory mechanisms.

Two procedures are useful: (1) the measurement of gastric juice obtained when no artificial stimulus has been used; (2) the examination of gastric juice obtained after stimulation with histamine.

TEST FOR BASAL GASTRIC SECRETION

Technic.—The patient is prepared as for a basal metabolism test: he should be at rest after a complete fast of twelve hours. A duodenal tube is passed and the gastric contents aspirated, as described later for the histamine test. Unless pyloric obstruction is present, from 10 to 50 cubic centimeters (rarely more) of turbid colorless or perhaps bile-stained fluid with a variable admixture of mucus will be obtained. Continuous suction is then kept up by means of a 50 cubic centimeter Luer syringe attached to the tube, and the material obtained is segregated in graduated tubes in portions obtained over successive ten minute periods. Aspiration is kept up for one hour. After a few periods, the flow of juice usually reaches a nearly steady level. The amount of juice obtained during a ten minute period after this point is reached, and its activity, are taken as the basal secretory values for that patient. Remarkably constant results are obtained for the same subject on successive days.

The values of basal secretion for healthy persons are as follows: ten minute secretory volume, 5 to 25 cubic centimeters; total acidity, 0 to 110 degress; free acidity, 10 to 30 degrees less than the total. The regurgitation of any large amount of bile vitiates the test, which must then be repeated on another day.

Pepsin.—For practical purposes there is no need for differentiating gastric anacidity from so-called achylia gastrica of the older writers (absence of acid and ferments). The actual facts are briefly these: When there is no free hydrochloric acid and the volume of gastric juice is reduced to a minimum of a few drops of mucoid material, peptic activity is, to all intents and purposes, absent. Under these conditions digestion is carried out successfully in the small bowel instead of in the stomach, and attempts to determine peptic activity by titration serve no useful purpose.[7]

Hyperacidity.—The term "hyperacidity" is loosely used by many physicians to designate a clinical syndrome featured by a feeling of fulness, gas and burning in the epigastrium, often associated with the eructation of sour material. It is assumed that because acid burns, a burning feeling in the stomach is due to too much acid. This is of course entirely erroneous, and this syndrome occurs, in fact, when the juice shows either high or low acidity. The degree of acidity probably has no direct connection with the genesis of the symptoms, which are mediated by motor disturbances such as pylorospasm. Detailed evidence for this position has been presented elsewhere.[2] It would be advisable to drop the term "hyperacidity" altogether and simply speak of high or low acidity, not on the basis of clinical symptoms, but on the basis of actual analysis of the gastric juice.

As a rule, the measurement of basal secretion suffices. However, if no free acid is obtained, one should proceed to the histamine test.

THE HISTAMINE TEST

Technic.—The patient is prepared as for the basal test. The tube is passed for a sufficient distance to allow its tip to reach the most dependent part of the stomach. The position of the tube may be maintained by strapping it to the angle of the mouth with adhesive. The patient is urged not to swallow saliva, and this caution is emphasized throughout the test. A vessel is furnished for expectoration. As soon as the tube is in place, the gastric contents are withdrawn with a syringe. A 50 cubic centimeter Luer syringe is most satisfactory. After the fasting secretions have been collected over two or three ten minute periods and have reached a minimum, histamine hydrochloride* (0.01 mg. per kilogram of body weight) is injected hypodermically to stimulate gastric secretion. This dose is adequate and produces no noteworthy constitutional symptoms, although a wheal is produced at the site of injection and some patients complain of a hot flushed feeling in the face and neck. After the injection of histamine, aspiration is continued over four to six ten minute periods.

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* A stock solution containing 1 mg. per cubic centimeter can be kept in the icebox and used for several weeks.

A certain amount of practice is necessary before the procedure can be carried out satisfactorily. At first, owing to the alternating phases of tone and relaxation to which the fasting stomach is subject, continuous aspiration is difficult, and one tends to traumatize the mucosa. After a little experience one's tactile sense develops so that the procedure becomes simple.

A possible source of error should be mentioned: in spite of continuous aspiration, one may not obtain all the gastric secretion; some material may pass out of the stomach even while suction is being done. In actual practice it seems unlikely that any large amount of juice is lost in this way, because the curves plotted from the volumes of juice obtained over a series of ten minute periods almost always show a regular form (Fig. 38). Furthermore, repeated tests of the same person yield almost identical results, which probably would not be true if a large and variable amount of juice were escaping through the pylorus.

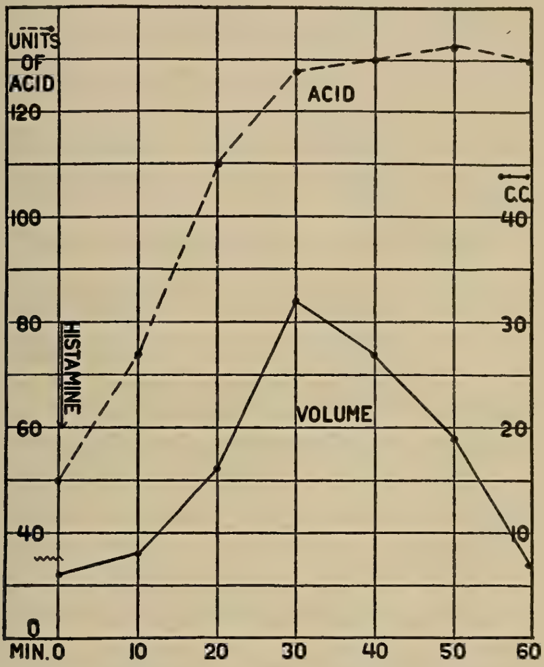

Fig. 38.—Curve of acidity and volume of secretion in a normal person after histamine stimulation. The total secretion was collected over ten minute periods. (Bloomfield and Polland, courtesy of *J. A. M. A.*[5])

If there is marked bile staining, the results must be discarded and the test repeated on another day. The aspirated material is normally a clear, limpid or slightly opalescent fluid containing more or less mucus, which can be removed readily by centrifugation. Such juice is suitable for chemical tests of all sorts.

Normal Volume.—The largest amount of gastric juide obtained during any single ten minutes after histamine administration varies in normal persons from 5 to 50 cubic centimeters. The latter value is only rarely exceeded. However, in the majority of cases, maximum ten minute secretion is from 15 to 40 cubic centimeters.

Normal Acidity.—The highest acidity (total) obtained during the test varies from 0 to 160 degrees, but for the majority of normal persons it lies between 80 and 130.

APPLICATIONS

In certain conditions practical diagnostic conclusions at times can be drawn from gastric secretory findings, They are, briefly, as follows:

1. **Duodenal Ulcer.**—Patients with duodenal ulcer or with a tendency to duodenitis and mucosal erosions usually show a large volume of highly acid juice. After histamine is given, the total acidity is often from 100 to 140 degrees. However, some normal persons without evidence of ulcer, past or present, also produce juice of this sort, so that no absolute conclusions can be drawn. In a doubtful situation, though, anacidity or a scant secretion of low acidity rules out duodenal ulcer, to all practical intents and purposes, even though a few instances of this disease with anacidity have been reported. Measurement of the *fasting or basal secretion* is especially helpful when duodenal ulcer is suspected, since acid values of from 110 to 140 are sometimes encountered and these are rarely if ever obtained for normal persons. It is safe to say that basal acidity over 110 indicates a duodenum liable to inflammation and erosion even if no ulcer happens to be present at the moment of examination.[3]

2. **Gastric Ulcer.**—This condition must be sharply distinguished from duodenal ulcer, as far as the findings in the stomach juice are concerned. The whole range of values found for normal subjects may be encountered with this condition: anacidity or a low acid level by no means rules out the lesion, and the high values characteristic of duodenal ulcer usually are not obtained. In summary, neither basal secretion nor the juice produced after administration of histamine yields any highly specific diagnostic information as regards gastric ulcer.

3. **Cancer of the Stomach.**—The old view that gastric anacidity means cancer of the stomach is now known to be incorrect. Modern studies[6] show that many healthy persons have practically no gastric secretion. Furthermore, Keefer and I[4] pointed out some years ago—and the observation was later confirmed by Vanzant and her colleagues[10]—that the frequency of gastric anacidity in normal persons increases with age. Thus, in the group over fifty—the very group in which gastric cancer is most likely to occur—20 per cent or more of the population will be found to have no free hydrochloric acid.[12] It is true that many persons with cancer of the stomach have deficient gastric acidity, since the growth probably often arises on the basis of an old gastritis with anacidity. Approximately one-fourth of the gastric cancers in my series,[1] however, were associated with the presence of acid, often in average amounts. Whether cancer with acid indicates a lesion which has arisen on the basis of an antecedent ulcer has been sharply questioned in recent years, although the matter is perhaps not finally settled. At any rate, the character of the gastric juice, except with the most extensive and destructive cancer of the stomach, may vary over the whole normal range and is of little help in diagnosis.

4. **Gastritis.**—In the past it was generally believed that gastritis, especially the extensive atrophic type, is invariably associated with gastric

anacidity or, indeed, with total absence of gastric juice. The whole subject has recently been thrown open again, however, by the introduction of the gastroscope. Gastroscopic studies have shown on occasion a normal looking mucosa in a patient with anacidity; conversely, an interestingly enough, some përsons with the gastroscopic appearance of gastritis seem to secrete an abundant and apparently normal juice. The final answer to the question waits on (1) the better understanding and diagnosis of the various forms of gastritis with the gastroscope and (2) correlation of the gastroscopic appearance with "normal" secretory findings as well as with definite absence of gastric secretion on successive tests, even after stimulation with histamine.

5. **Systemic Disease.**—Gastric secretion may fail in the presence of various wasting conditions and of certain endocrine disorders. Practically, however, pernicious anemia is the outstanding disease aside from local stomach conditions in which the study of the gastric juice is of importance. As every physician knows, normal gastric secretion does not occur with this disease.[13] Hence, presence of free acid rules out true Addisonian anemia, although acid may be obtained in subjects with certain somewhat similar macrocytic anemias, such as sprue.

6. **Fever.**—It is worth remembering that gastric secretion is much diminished during fever, from whatever cause. There is often complete anacidity. Suppression of gastric secretion by "artificial" fever is promptly followed by return to normal when the temperature falls.[14]

CONCLUSIONS

Analysis of the gastric secretions usually gives little or no information of clinical use. In certain special situations—for instance, when duodenal ulcer or pernicious anemia is suspected—determination of gastric acidity may be helpful. "Routine" gastric analysis is a waste of time; the procedure should be reserved for the occasional case in which useful information may be obtained.

The simplest method is the examination of gastric juice aspirated over successive ten minute periods under basal conditions without any special meal or stimulus. This may be supplemented by the further study of juice obtained after the ingestion of histamine, which gives a maximal stimulus for secretion. Studies of pepsin, lactic acid and the like serve no useful purpose in general clinical work.

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11. See Reference 6, p. 8.
12. See Reference 6, p. 53.
13. See Reference 6, p. 108.
14. See Reference 6, p. 187.

CHAPTER VIII

GASTRITIS

INTRODUCTION

Gastritis is an inflammation of the gastric wall, especially of the gastric mucosa. It is an anatomic designation of complex anatomic changes, usually called inflammatory, within the gastric wall. In chronic inflammations, such as those of the kidney, the character of these changes as defense mechanisms of the body often cannot be established, and therefore it is necessary to define as inflammation of these organs merely the anatomic condition which may be recognized at microscopic examination. The cause of these changes may be varied.

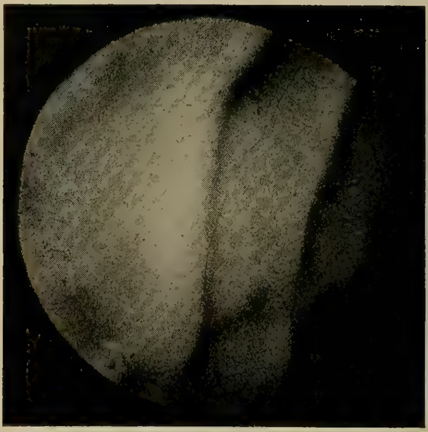
Inflammation in the histologic sense has nothing to do with infection. It may well be due to allergy, and even the possibility of psychogenic origin must be admitted, although no real evidence of this is available as yet. However, the uniform, unmistakable histologic picture would force one to call the consequences of either allergy or psychic disturbance inflammation, *i. e.*, gastritis.

Gastric ulcer, gastric carcinoma and gastritis form the three major diseases of the stomach. The relative incidence is approximately: 9 (gastric ulcer):7.5 (gastric carcinoma): 45 (gastritis). However, duodenal ulcer is not included in these figures, and if gastric and duodenal ulcer should be included as "chronic gastroduodenal ulcer," the frequency of this disease would be about the same as that of gastritis.

The diagnosis "gastritis" was abhorred for over a century, because the gastric mucosa disintegrates rapidly during and after death, so that no conclusion concerning its condition before death can be drawn by the pathologist. For some time it was thought that fresh material gained by gastric resection would yield sufficient information, but it was found that even during the relatively short act of resection, artefacts of the gastric mucosa would originate, simulating inflammation.

Convincing proof of the frequency of gastritis was brought out by the direct observation of the gastric mucosa which became feasible by the advance of gastroscopy, and especially by the invention of the flexible gastroscope (see Appendix, p. 179). The gastroscope permits observation of the healthy stomach as well as repeated examination of the stomach in the presence of epigastric distress, thus making possible not only the description of the diffuse mucosal alterations, but the following of the course of the disease, the comparison between morphologic findings and subjective complaints and the observation of the effects of therapy. Gastroscopic examination, however, will rarely be carried out in the presence of acute disease, and therefore only the section of this chapter on chronic gastritis will be based chiefly on gastroscopic conceptions.

Recently it has become possible to establish the histopathology of chronic gastritis. The method used for obtaining unobjectionable histologic material consists of taking biopsy specimens from the gastric wall without the use of ligatures or clamps when laparotomies are carried out on patients who previously have been examined gastroscopically. Sometimes the "formalin injection method," introduced by Faber, consisting of injection of formalin into the abdominal cavity immediately after death, yields satisfactory results.



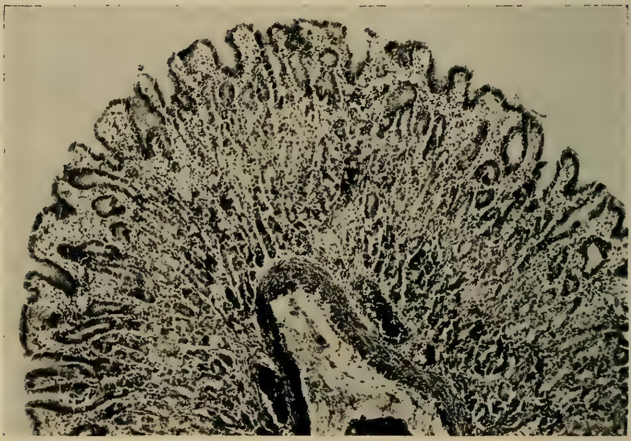


Fig. 39.—*A*, gastroscopic picture of the normal gastric mucosa (made through the rigid Schindler gastroscope of 1923, with Henning's photographic attachment). Parallel and cross folds are seen in a smooth surface. *B*, microscopic section through the normal body mucosa, showing regular surface epithelium and rather shallow crypts. The long body glands are close together; only scant interstitial cells are seen.

ACUTE GASTRITIS

Acute gastritis may be subdivided into four types: (1) simple exogenous, (2) corrosive, (3) infectious (hematogenous) and (4) phlegmonous. The first two forms are exogenous, the last two hematogenous.

Acute Simple Exogenous Gastritis (acute gastric catarrh; acute gastrosis; food poisoning).—Acute simple exogenous gastritis is frequent at all ages and is characterized by severe malaise, anorexia, nausea and vomiting. Its duration is one day to one week. Frequently concomitant enteritis is present. The expression "food poisoning" is inadequate. In numerous instances an inflammation develops as a reaction to ingested food which is neither spoiled nor a poison in itself (especially alcohol and spices). In cases of toxic disease due to *Bacillus paratyphoid B* or *Bacillus enteritides Gaertner*, the diagnosis "general infection by Bacillus paratyphoid B," etc., should be made. The character of acute simple exogenous gastritis as an inflammation of the stomach has been established gastroscopically.

Pathologic Anatomy.—Since patients do not die from this form of acute gastritis, the histologic picture is unknown. Because of the rapidity with which symptoms develop, it has been assumed (Katsch) that often there is no anatomic foundation, but that the disturbances are functional; the term "gastrosis" has been used for this reason. This assumption, however, never has been proved and even seems to be unlikely. It is known that irritation may produce an inflammatory tissue reaction within an astonishingly short time, and since the symptoms start usually several hours after the etiologic irritation, the presence of acute inflammation can safely be assumed. Nothing would even be known about the gross anatomic changes if the classic description of Beaumont and a few gastroscopic observations were not available. Beaumont saw, through the fistula of his servant, red patches, aphthous patches and slimy white mucus after excessive eating or drinking. The next observation of the gastric mucosa in the presence of simple exogenous acute gastritis was published in 1923 by Schindler, who examined a patient gastroscopically on the second day of the disease and found the mucous membrane covered with a thick vitreous mucus. Henning also found thick mucus and, in addition, reddening of the mucosa and occasional hemorrhages, and these signs outlasted the subjective symptoms of the patient.

Symptomatology.—The symptoms start six to forty-eight hours after the etiologic irritation. The patient loses his appetite and feels epigastric pressure and fulness and sometimes also epigastric pain. Attempts to relieve the pressure by belching are without result. Nausea develops, often accompanied by headache and a slight rise of the temperature. Then copious vomiting of slimy, often sour material and food remnants, rarely mixed with blood, occurs once or twice. After that the patient feels thoroughly relieved, but then the most characteristic symptom, severe prostration, becomes apparent. He has to lie down and is unable to do any kind of work. No explanation has been found for this symptom, which sharply contrasts with the entire lack of objective findings. However, a similar symptom will be encountered in some forms of chronic gastritis. Therefore, endocrinologic factors, especially some relation to the adrenal glands, have been considered. Disagreeable taste and odor of the mouth are noticed. If diarrhea occurs, concomitant inflammation of the intestine must be assumed to be present.

The objective symptoms are few. Fever, if present, is low and of short duration. Some tenderness of the epigastrium may be present. The motor activity of the stomach is impaired, first inhibited and then accelerated. Its secretory function varies widely, with a tendency toward hyperacidity. Lactic acid may be found in the stomach contents. Microscopically, leukocytes and epithelial cells are found. The urine may show increased amounts of urobilinogen, which then indicate participation of the biliary tracts in the inflammation. This is important, and since the "aldehyde test" can be carried out easily, the practitioner should not omit it. Some drops of Ehrlich's aldehyde reagent are added to the urine. Outspoken red color in transparent light indicates a pathologic amount of urobilinogen. Leukocytosis has not been described.

Typical x-ray findings do not exist. Although gastroscopy reveals characteristic signs, it is an unnecessary strain for the prostrated patient.

Diagnosis.—The diagnosis usually is easy. If fever is present, beginning typhoid fever may be suspected, and the developments of the next day will usually make the diagnosis clear. Agglutination tests may be used, although they are usually unnecessary. Occasionally symptoms suggestive of an abdominal catastrophe (perforation) may be caused by acute gastritis in alcoholic persons.

Course and Prognosis.—This disease lasts from one to eight days. However, even when the subjective symptoms are gone, general weakness will be present for some more days, or even weeks. Gastroscopic observations have taught that this symptom is due not only to the insufficient intake of food but to the persistent inflammatory changes of the gastric mucosa. In the great majority of cases healing occurs without any after-effects. Therefore, the prognosis is a good one. However, there are two threatening dangers. In a great many cases chronic superficial-atrophic gastritis (*vide infra*, p. 164) develops from insufficiently treated simple exogenous acute gastritis. This can and should be prevented. Concomitant ascending cholangitis, characterized by a strongly positive aldehyde reaction, is a rare but disagreeable complication. I observed a fatal end in one case, with the following sequence of events: simple exogenous acute gastritis, subacute superficial gastritis for one month, ascending infection of the biliary tracts for two months, severe icterus and subsequent death in the fifth month. The case was checked by autopsy. These two complications strongly suggest the inflammatory character of the primary disease.

Therapy.—Some patients are not able to vomit spontaneously. Vomiting may be induced by the drinking of a glass of warm water. Emetics should be avoided. Rarely will it be necessary to perform a gastric lavage. If the patient cannot vomit, however, he will greatly appreciate this procedure. Also, a large edema has an agreeable immediate effect. For concomitant enteritis, a laxative should be given. Castor oil, the mildest one, is usually abhorred by the patient. It may be replaced by compound licorice powder (1½ teaspoonfuls* in some water) or by citrate of magnesia (½ bottle*), which is readily taken because of its refreshing content of carbonic acid. Even if the patient sees the doctor only after several days of diarrhea, no opiate should be given without a preceding laxative. During the days of acute illness the patient needs complete bed rest. Hot applications, especially an electric heating pad, are agreeable. The abstinence from food should be absolute on the first day. The patient, being totally anorectic, will always consent. Fluid, however, should be given. Hot tea with sugar and mineral water, especially Vichy water, should be taken in sufficient quantities. In those rare cases in which the stomach is exceedingly irritable, dextrose enemas may be administered. On the second day cream soups should be given, also bouillon with some salt, especially if a loss of chloride by abundant vomiting or diarrhea must be made up. From

* All doses given are for adults.

the third day on, toast with some butter, soft boiled eggs (three or four minutes), rice and farina are permitted. Then tender meat, chicken, squab, brain, sweetbreads and hashed veal, with mashed potatoes may be tried. The chief duty of the physician is to induce his patient to stay on such a diet for at least one week after the disappearance of the subjective symptoms, in order to avoid the transition into chronic gastritis. Drugs should be avoided entirely with the exception of the mentioned laxative. Bed rest is necessary for only one or two days, but should be continued if a strongly positive aldehyde reaction is present.

Acute Corrosive Gastritis.—**Etiology.**—This form of acute gastritis is also due to "exogenous" factors, not to food but to corrosive substances such as acids and lyes, introduced into the stomach either by error or by suicidal intention. Most frequently observed are hydrochloric acid, sulfuric acid, oxalic acid, acetic acid, nitric acid, formic acid, further caustic lyes, corrosive mercuric chloride, silver nitrate and arsenic.

Pathologic Anatomy.—Corrosive substances produce necrosis with formation of scabs and a subsequent inflammatory reaction. The appearance of the scabs varies according to the kind of poison used; this can be observed best in the mucosa of the mouth, but the same phenomenon is found in the stomach. Black, dry scabs are produced by sulfuric acid; black-brown ones, by hydrochloric acid; yellow ones, by nitric acid, and white, by acetic and by oxalic acid. Lyes cause transparent swelling. In some cases the necrosis is found only on the ridges of the gastric folds; in others only the antrum is involved. Mucosal hemorrhages are seen frequently. Microscopically, there may be observed a rapid inflammatory tissue reaction consisting of invading plasma cells and of leukocytes migrating through the epithelium. If the condition heals, sometimes the picture of atrophic gastritis develops (*vida infra*, p. 170).

Symptomatology.—The symptoms of corrosive gastritis are general and local. The general symptoms are: severe collapse with cool skin, faint frequent pulse and cyanosis. Locally, severe epigastric burning and cramplike pain are always present. Corrosion of the mouth and esophagus leads to dysphagia, which makes swallowing of solid food impossible. The thirst, however, is so torturing that the patients frequently make attempts to drink. Objectively, the characteristic scabs may be found on the skin of the face, on the lips and in the mouth. Bloody vomitus and quickly occurring bloody stools are rather characteristic. The epigastrium is tender, and there is rigidity of the abdominal musculature, which may become intense if perforation is imminent or has occurred. The day after the poisoning, albuminuria will be found; casts are present, and the amount of urobilinogen often is increased. *X*-ray examination is rarely feasible. Cancer-like filling defects of the antrum have been demonstrated. Gastroscopy is contraindicated. However, Henning examined three girls gastroscopically twenty-four hours after they had ingested relatively small amounts of oxalic acid. The gastric mucosa was found to be reddened and moist, and the folds appeared to be broader than normal; ecchymoses of the ridges were seen; the antrum mucosa was covered with thick, milklike slime. I examined a girl four weeks after she had drunk concentrated hydrochloric acid, when a pyloric stenosis developed; the antrum was swollen and reddened, and small erosions were still visible.

Diagnosis.—History and the objective findings on the lips and in the mouth render the diagnosis easy. However, white scabs produced by acid have been confused with genuine diphtheria.

Course and Prognosis.—Death occurs frequently from collapse or from perforation peritontitis. The acute dangerous stage may last two or three days, after which the intake of food will become possible. However, frequently chronic gastritis develops, and this leads either to atrophy or to thickening of the gastric wall and obstruction of the pylorus. The final prognosis depends on the existence of these complications and on the condition of the esophagus (see p. 88 *et seq.*).

Therapy.—The fate of the patient often depends on rational and energetic therapy. The mortality has been reduced from 33 to 3.8 per cent when treatment is early. The initial collapse must be treated energetically. One cubic centimeter of metrazol should be administered subcutaneously every hour. Morphia—or for children codeine—should be given in sufficient doses (for adults not less than 0.02 Gm.). The chief question is that of immediate lavage. Formerly one was afraid of causing perforation by introducing a stomach tube. Extensive experience, however, has shown that this danger is minimal. Perforation can occur only if the gastric wall is softened so thoroughly that spontaneous perforation would have occurred anyway. On the other hand, the results of immediate lavage are so gratifying that it should be omitted only if intensive muscular abdominal rigidity points toward imminent perforation. The tube (French 27 to 34; German 9 to 12) should possibly have no hole at its tip but only lateral windows. The water should be tepid. If the effective poison was an acid, milk, albumin or limewater may be added; for corrosion by lyes, weak acids (citric or acetic acid) may be used. Naturally such lavage should be undertaken as soon as possible. In the first few days no attempt at giving food should be made. The torturing thirst will be alleviated by the administration of drip enemas of dextrose solution.

Perforation and later pyloric obstruction require surgical interference. The extremely important management of the corroded esophagus has been discussed in the chapter on that organ (see p. 88). Therapy of late chronic gastritis and atrophy follows the rules of therapy of chronic atrophic gastritis (*vide infra,* p. 175).

Acute Infectious (Toxic)*-Gastritis.—**Definition.**—The expression designates a form of acute gastritis originating by the influence of toxins or bacteria entering the stomach from the blood stream (hematogenous origin). The best description of this disease has been given by Knud Faber.

Etiology.—Hematogenous gastritis is found with measles, scarlet fever, sepsis, diphtheria, influenza, pneumonia, variola, typhoid and yellow fever. Sometimes bacteria may be found in the gastric wall (typhoid, sepsis); usually bacterial toxins are the causative factors.

Pathologic Anatomy.—This gastritis is a "pangastritis" spreading over the entire stomach. Often severe hemorrhagic inflammation is found. Erosions are frequent. Microscopically, a dense leukocytic infiltration is seen.

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* In former times the expression toxic gastritis was used sometimes instead of corrosive gastritis. This term is ambiguous. The word toxic should be reserved for manifestations caused by toxins in the bacteriologic sense of the word.

Symptomatology.—There is little doubt that the severe anorexia of influenza and other infectious diseases is due to this type of gastritis. Vomiting and sensations of pressure in the epigastrium are less frequent than with other types. However, hematemesis may occur, especially with influenza, and may even become dangerous.

Diagnosis.—Hematogenous infectious acute gastritis may be diagnosed when with infectious disease anorexia or vomiting is present.

Course and Prognosis.—In the most severe form, observed with influenza, the appetite begins to improve after one week. The prognosis is good. Death from hemorrhage is a rarity. Microscopically, remnants of the disease are always found. However, it never has been proved that true chronic gastritis develops from hematogenous infectious acute gastritis.

Therapy.—The patient in refusing to eat takes good care of his stomach. Nevertheless, starvation must not be permitted, and continuous attempts to institute a bland "fever diet" should be made, especially if the course of the underlying disease is protracted. In the beginning, often stewed fruits, especially cooled apple sauce, and icecreams are accepted. As soon as possible, milk, cream, eggs, rice and farina boiled in milk and gruels with butter should be tried. Often slightly spiced soups are preferred. Jellies of meat or of fruits are recommendable. Later, hashed soft meat, chicken, mashed potatoes and zwieback should be given. Some authors recommend alcohol, especially port wine, sherry, etc., during the first stage of the disease. Fruit juices and lemonades, however, are better drinks. No other therapy is necessary; drugs, if necessary for the therapy of the primary disease, should be administered subcutaneously or rectally.

Acute Phlegmonous Gastritis.—Definition.—This is a purulent diffuse or localized inflammation of the gastric wall. It is a rare disease.

Etiology.—In most cases bacteria were found to be causative, especially streptococci, also staphylococci, *Bacillus coli* and others. In some cases the infection originated from a gastric ulcer or a gastric carcinoma and in others from a gastric lesion or a gastric foreign body; most frequent, however, are metastatic hematogenous infections with sepsis, endocarditis, cystitis and infectious diseases (variola, typhoid).

Pathologic Anatomy.—In the localized form, an abscess is found in the gastric wall. In the more frequent diffuse phlegmon, the entire gastric wall, chiefly the submucosa, is thickened. Microscopically, purulent inflammation, leukocytes, necroses and large numbers of bacteria are seen. Thrombophlebitis is present and may proceed into the portal vein.

Symptomatology.—The symptoms are those of an acute severe abdominal infectious disease. Chills, intensive epigastric pain, high fever and vomiting are present. Objectively, the picture of a dangerous peritoneal disease is found: there are severe prostration, dry tongue, high fever, weak and rapid pulse, cyanosis of the extremities and accelerated respiration; the abdomen is meteoristic and tender, and outspoken rigidity is present. The vomitus only rarely contains pus. Diarrhea occurs. Slight icterus may be observed. The fever shows septic remissions. In the blood a leukocyte count of 20,000 to 30,000 is found. *X*-ray findings have not been described. Gastroscopy is contraindicated.

Diagnosis.—Except in the rare cases in which a localized abscess leads to purulent vomitus, the differentiation from localized peritonitis following ulcer perforation, purulent cholecystitis and acute necrosis of the pancreas is difficult or impossible.

Course and Prognosis.—Most patients die within a few days. Spontaneous healing, if possible, seems to be very rare. Surgical interference improves the prognosis considerably.

Therapy.—The therapy should be surgical. The symptoms of a severe abdominal disease with fever often will lead to surgical interference, even without exacting diagnosis. Then a localized abscess may be opened and drained. In the cases of diffuse phlegmon gastrectomy may lead to complete cure.

CHRONIC GASTRITIS

Classification.—This section is based chiefly on *gastroscopic observations*. Exact knowledge of the normal mucosa of the healthy adult is a prerequisite to any diagnosis of diffuse alterations. The following gastroscopic signs have not been found in healthy stomachs: patchy reddening; swollen edematous appearance of some area or fold; adherent secretion; patchy or diffuse thinning; greenish-gray or gray discoloration of the mucosa (often combined with increased highlights); the appearance of bloodvessels; swollen, spongy dull appearance of the mucosa (recently, however, Fitzgibbon found some swelling of the mucosa in 2 healthy adults among 40 observed); formation of granules, nodules, nodes, verrucas; stiffness, irregular thickening and segmentation of folds; mucosal hemorrhages; superficial erosions and ulcerations. When such changes are seen gastroscopically, microscopic examination invariably proves that severe inflammatory changes of some kind are present. If a normal mucosa is found gastroscopically, a normal microscopic picture is usually seen also. It follows that the positive gastroscopic diagnosis is reliable and the negative usually is reliable also, although sometimes gastritis may be overlooked. Some diffuse changes cannot be classified as inflammation.

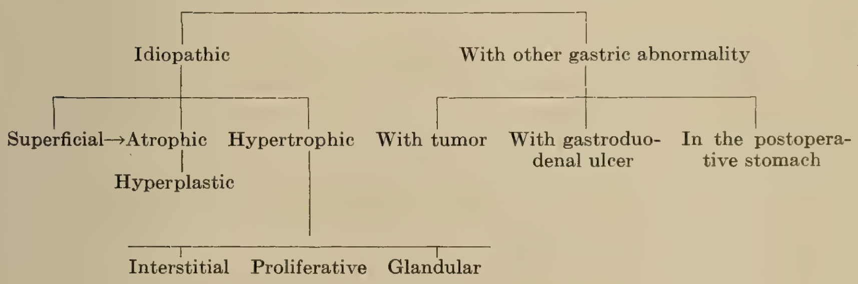
After my first gastroscopic studies in 1921 it seemed rather obvious to me that some of the changes seen were rather superficially located, "catarrhal" and prone to heal; that others were the expression of a general thickening of the mucosa, and that in a third group there was thinning of the mucosa. In all three groups, local alterations such as hemorrhages and erosions were rather common, and it did not seem appropriate to classify "hemorrhagic" or "erosive" gastritis as a separate group. (The entity of "erosive gastritis" is still upheld by some authors, especially by Henning.) Later a definite relation was found between the superficial catarrhal and the atrophic changes. Sometimes they appeared in the same stomach, but more frequently atrophic gastritis followed superficial gastritis. Such a relation usually could not be observed in the presence of a thickened mucosa, diagnosed as hypertrophic gastritis, but among about 2,500 cases of gastritis, occasionally atrophic changes were seen together with hypertrophic ones. This occurred so rarely that a relation between hypertrophic gastritis remained stationary or improved, but would neither heal nor develop into atrophy. Therefore, hypertrophic gastritis was considered to be a clinical entity different from the superficial-atrophic type. This differentiation received its most valid confirmation from the discovery that microscopic pictures corresponded with the gastroscopic findings. And it now seems that this classification has been generally accepted.

The specific cause does not seem to affect the anatomic picture, whether superficial-atrophic gastritis follows acute exogenous gastritis, a focal infection, a deficiency state or abuse of alcohol; always the identical and typical gastroscopic and microscopic pictures are seen. (This is not so if chronic gastritis is seen in a stomach involved by another disease: the ulcer-bearing stomach, the tumor-bearing stomach and the postoperative stomach often present pictures in which all forms of gastritis appear together.) Thus it becomes necessary to differentiate between chronic gastritis with concurrent gastric abnormalities and the more common gastritis with no other gastric disease, called chronic idiopathic gastritis.

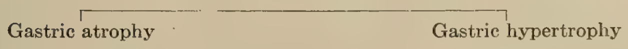
An inflammation may lead to an end-stage in which the disease proper is healed but in which the tissue affected has been altered permanently with or without important change of its function. Such end-results of disease have been called "-pathias" by Aschoff, and in the case of the stomach they would have to be called "gastropathias." Surprisingly, even when mere degeneration would be expected (deficiency states) true inflammation may be seen. Then, however, as well as when another form of atrophic gastritis is present, the final clinical and microscopic picture may show only atrophy without inflammation. This, however, is often not easy to decide, and sometimes when the mucosa is entirely atrophic, signs of active inflammation may still be observed microscopically. It can almost never be stated with certainty that chronic inflammation has come to a definite end, although Chester Jones has emphasized the existence of noninflammatory atrophies. Theoretically, noninflammatory hyperplasias could exist as well, and some cases observed suggest such a possibility, although in all of them evidence of real inflammation has been found. It has seemed wise not to separate gastropathias entirely from chronic gastritis but rather to put them into a sepeculative annex, which is discussed at the end of this chapter.

Some lesions may not belong under inflammation, such as hemorrhagic erosions, mucosal hemorrhages and pigment spots in the noninflamed mucosa, as seen for instance in generalized purpura. Microscopic confirmation of the gastroscopic observations is not yet available for these.

CHRONIC GASTRITIS



Annex
GASTROPATHIAS



Attempts have been made to include localization and function in a classification. The question of localization of gastritic changes previously seemed of great importance (Konjetzny) but now we know that with "antral gastritis" the body is almost always involved also, and that certainly neither antral gastritis nor body gastritis is a disease entity. Gastric function in all types of gastritis is so irregular and equivocal that it cannot be the basis of classification. The final classification, based on gastroscopic and histologic observations, will be found in the chart (p. 165).

Gross Anatomy.—Conclusions concerning diffuse changes drawn from the inspection of the gross specimen of a stomach should usually be avoided. Gray opaqueness, diffuse reddening, formation of small regular nodules, mucosal hemorrhages and even superficial erosions in the postmortem specimen are meaningless. Formation of large inflammatory pseudopolyps, verrucas and inflammatory pseudotumors, and especially severe smoothness and atrophy of the gastric mucosa, may be correctly diagnosed in rather rare instances.

Etiology.—The cause in most cases of chronic gastritis is unknown, and therefore etiologic considerations will be discussed generally for all forms of gastritis. The concomitant occurrence of any other disease with chronic gastritis does not establish the etiologic relation. Gutzeit and Teitge have furnished an extensive compilation of all possible etiologic factors, but have not offered evidence for the significance of any of them.

Bacteria.—As long as the stomach contains hydrochloric acid it is practically sterile. The achylic stomach contains an enormous number of bacteria, and it has been assumed that primary achylia will lead to secondary infection and inflammation. Although this is possible, another sequence seems to be more likely, namely, that primary inflammation leads to secondary achylia and to invasion of the stomach by bacteria.

Focal Infection.—Often infection of the sinuses and of the teeth have been observed with gastritis. However, these are frequent diseases, whose concurrent presence may be incidental. It has been assumed that postnasal drip may lead to gastritis.

Deficient Teeth.—Teitge did not find any connection between the condition of the teeth and gastritis.

Irritation by Alcohol and Nicotine.—For thirty years gastritis was considered indicative of alcoholism. Extensive studies by Gray and Schindler and by Berry in persons with severe chronic alcoholism have recently demonstrated that even daily ingestion of a tremendous amount of any kind of alcoholic beverage does not necessarily lead to chronic gastritis. In half of their cases, a normal gastric mucosa was found. In the other half, chronic superficial-atrophic gastritis was present. This is still more than would be expected among healthy persons, and thus alcohol may contribute to the origin of chronic gastritis, but there must be a second etiologic factor, the nature of which is not yet known. The alcoholic persons with normal stomachs did not differ decisively from those with gastritis in their consumption of tobacco or in their diet. Most gastroscopists believe that misuse of nicotine may lead to chronic gastritis, but this has not been proved.

Use of Condiments, Spices and Drugs.—Spices most definitely may cause severe acute simple exogenous gastritis. Therefore, one might think that their chronic misuse might produce chronic gastritis too, but this has never been proved. English authors have found that aspirin produces mucosal hemorrhages in the gastric mucosa, but recently Paul, after extensive investigation, was not able to confirm this.

Metals.—Gutzeit observed severe chronic superficial gastritis after lead intoxication, and bismuth and arsenic also may lead to superficial gastritis.

Deficiency States.—Unquestionably some deficiency states may lead to gastritis, not necessarily the atrophic type. The etiologic significance of lack of iron, of Castle's autianemic factor and of vitamin A or B have been considered.

X-ray Irradiation.—This has been proved beyond doubt to be a factor in the origin of a peculiar gastritis.

Acute Gastritis.—Careful taking of histories will show cases of chronic gastritis in which acute simple exogenous gastritis initiated the disease picture. My expectation of finding this same sequence for acute infectious hematogenous gastritis has not been fulfilled; in only one case severe chronic hypertrophic ulcerative gastritis developed during influenza.

Allergy.—The influence of allergy on the condition of the gastric mucosa has not yet been studied adequately. There is a definite possibility that allergic gastritis exists.

Psychic Factors.—The fact that emotions may alter the appearance of the gastric mucosa has been demonstrated recently by Wolf and Wolff. The production of true inflammation from psychic causes has not yet been proved, but at least the possibility of reversible superficial inflammatory changes must be admitted. Microscopic checks seem to be lacking at the present time.*

Symptomatology.—Since the century-old fight about the existence of gastritis has been settled, a new and equally vehement disagreement now rages about the symptomatology of this disease. Physicians are accustomed to attribute local symptoms to local anatomic changes. The symptoms often are not permanent, although the anatomic lesion persists apparently unchanged. Why symptoms come and go without apparent reason is a matter of research. In some diseases no easy explanation can be found—for instance, in the case of tabetic crises: The degenerative changes in the cord are present continuously, while the pain comes in attacks only. In other diseases some plausible explanation may be found: In severe gallbladder attacks, for instance, one may postulate the influence of emotions or of dietary indiscretions, but in many instances no real explanation for the presence or absence of attacks can be found. Why in the same patient a gastric ulcer sometimes is silent and sometimes causes severe symptoms is not known, and the assumption of modification of the pain threshold by various influences is mostly speculative. If in chronic gastritis the symptomes are most capricious, sometimes absent for many years and then suddenly recurring, then perhaps either local anatomic changes, such as mucosal edema, or psychic factors may be the cause for the difference in the disease picture, or the physician may speculate about modification of the pain threshold. It seems better, however, to admit that the reason is not yet known. In chronic gastritis the severity of the symptoms is not in agreement with the extent of the anatomic changes, and even deep extensive gastritic ulcerations do not necessarily produce pain. However, this discrepancy is common: The small boil of the skin will cause pain, while a large carcinoma of the same area may not. A small gastric ulcer may produce severe pain, while a large carcinoma of the same region may not. The fact, brought forward as early as 1926, that suggestion often relieves the symptoms of gastritis, holds equally in many other organic diseases: The anorexia of gastric carcinoma may often be cured psychologically; a severe toothache often has been cured, at least transitorily, by hypnosis; it is well known that the symptoms of whooping cough or of multiple sclerosis respond beautifully to some kinds of psychotherapy, and no one will consider this proof of the psychogenic origin of the symptoms of multiple sclerosis. Thus, the unwillingness on the part of some workers to accept the gastric symptoms associated with chronic gastritis as symptoms of chronic gastritis is a carryover from former times. Primarily it is necessary to consider symptoms as produced by the local anatomic changes, and although it must be admitted that a condition underlying the chronic gastritis (a deficiency state, for instance) or a concomitant disease (enteritis or colitis) may be chiefly responsible for many symptoms, up to the present time no conclusive proof has been advanced. The special symptomatology will be discussed under the special forms of chronic gastritis.

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* The frequent appearance of hypertrophic gastritis on roentgen examinations suggests that psychodynamic factors may play a more important role. This incidence in patients suffering from psychosomatic complaints cannot be underestimated. Further exploration of this phase will receive its due importance as gastroenterologists become acquainted with the psychogenic aspects of gastrointestinal disorders.—EDITOR.

Gastritis and the Military Services.—After the first World War there were veterans, obviously neither malingerers nor psychoneurotics, who complained about epigastric distress when there were no objective findings. When they were examined by means of the old rigid gastroscope, many forms of gastritis were discovered. These were held responsible for the symptoms, and compensation was granted to the bearers. The frequency and importance of symptom-causing chronic gastritis among the soldiers of the present world conflict has not yet been established definitely, as the use of the gastroscope within the army only now is beginning to spread. Kantor, who made extensive study of gastric sufferers in the first World War, has stated that "positive evidence of gastritis in a front line soldier should entitle him to every consideration and to every benefit that a grateful people can bestow upon its tried and proven defenders."

Chronic Superficial Gastritis.—This disease is a chronic inflammation of only the uppermost portion of the gastric mucosa, and comprises 26.5 per cent of all chronic gastritis.

Pathologic Anatomy.—Marie Ortmayer and I have devised a method of taking biopsy specimens from the gastric wall without the use of ligatures and clamps, and have succeeded in demonstrating the histopathology of this disease, which until recently has been known only from gastroscopic observations. The chief feature is the extensive edema found beneath the surface epithelium between the pits, which increases the thickness of the mucosa considerably. Within the edema a more or less extensive net of thin threads of fibrin is found. The capillaries crossing the edematous area are definitely enlarged. Extravasation of red blood cells is seen, and on the top of small hemorrhages there may be an interruption of the continuity of the surface epithelium (erosions). Among the cellular elements of the edema, plasma cells predominate. Cells of the surface epithelium may present an increase in the amount of mucus, which flattens and even excavates the nucleus (Fig. 40).

Gastroscopic observations show that chronic superficial gastritis may be found in any portion of the stomach. It is more frequent in the body than in the antrum. There are three characteristic signs: (1) patchy redness (hyperemia) or reddening of ridges of folds; (2) edema, presenting a characteristic "watery" appearance, and (3) exudation, the most characteristic sign. Adherent sticky mucus is observed. Sometimes the secretion is purulent. Mucosal hemorrhages and small erosions are frequent.

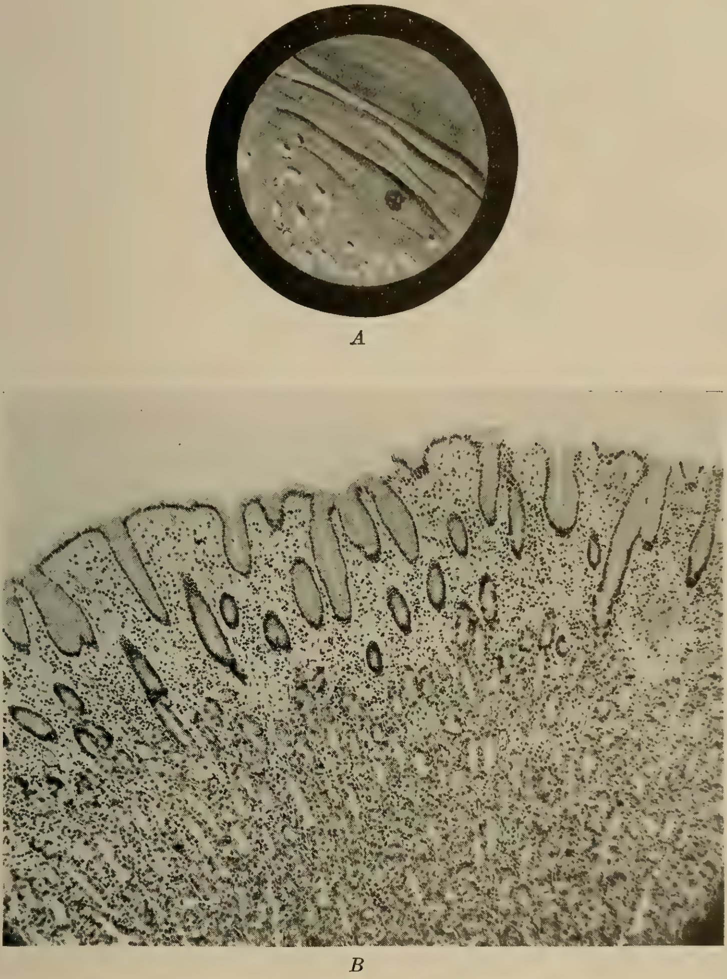


FIG. 40.—*A*, gastroscopic view in a case of chronic superficial gastritis. In the left upper quadrant adherent layers of mucus are seen. In the right lower quadrant marked patchy reddening is present, and there is one dark red superficial erosion. *B*, microscopic section through the gastric mucosa in a case of severe chronic superficial gastritis. Extensive edema between the pits, containing many plasma cells, enlarged capillaries and some extravasation of blood. The surface epithelium shows "catarrh": The epithelial cells are stuffed with mucus, which compresses and flattens the nuclei.

Symptomatology.—The symptoms of the superficial form, as well as of the other forms, are rather vague. The disease occurs at every age. Frequently ulcer-like delayed epigastric pain and night pain are present, and sometimes epigastric pressure and fulness occur. Nausea and vomiting have been mentioned; complaints of headache are common. The bowel movements are regular, diarrhea pointing to concomitant enteritis. The appetite often is poor; loss of weight may occur. Gross hemorrhages from superficial erosions have been observed.

Physical abnormalities are often entirely absent. Rarely a tender zone at the left side of the navel may be found by palpation; when checked fluoroscopically, this proves to represent the silhouet of the stomach itself. This zone may be brought out by palpating gently from the left iliac crest to the umbilicus and by noting that the patient suddenly moves as if a tender area has been palpated. On being questioned, however, he usually states that the sensation was not one of "real pain," but of a "different" character, difficult to explain.

Laboratory tests are usually not characteristic. Anacidity as well as hyperacidity may be found when the stomach contents are examined. The amount of mucus-containing cells may be increased. Sometimes occult blood is found at the examination of the stools. Of some importance is the finding of an increased amount of urobilinogen in the urine by the simple aldehyde test of Ehrlich. A positive result suggests concomitant involvement of the liver and excludes mere psychoneurosis.

X-ray examination may discover or confirm the tenderness of the silhouet of the stomach. There are no other *x*-ray signs of chronic superficial gastritis.

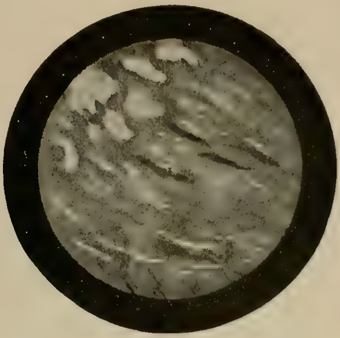
Diagnosis.—The disease may be suspected if after an attack of acute gastritis continuous gastric symptoms are present. The finding of tenderness of the gastric silhouet, together with a strongly positive aldehyde reaction of the urine, may suggest this disease. In most cases, however, the differentiation from other, more severe forms of chronic gastritis, from beginning carcinoma, from chronic gastroduodenal ulcer and from psychoneurosis is impossible without the combined use of *x*-ray examination and gastroscopy. The typical gastroscopic picture is diagnostic.

Course and Prognosis.—The condition may heal rapidly and completely, especially under adequate treatment. There is no tendency toward recurrence. Rarely does the condition remain stationary, especially if the patient fails to take care of himself; finally, it sometimes develops into atrophic gastritis, unfortunately. Sequelae and concomitant diseases will be discussed in a separate section (see p. 177).

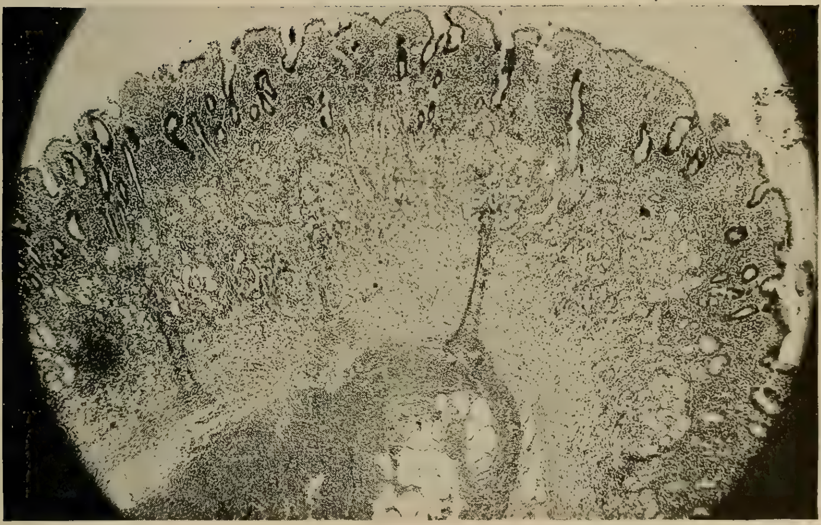
Therapy.—In order to avoid transition into atrophic gastritis, the treatment should be energetic. The degree of involvement of the mucosa might be ascertained with the gastroscope. If erosions are present, complete bed rest for about one week is indispensable. During this time the diet should consist only of fluids. Without evidence of the presence of erosions, bed rest is not necessary. Gastric lavages should be carried out every morning over a long period. Most patients learn quickly to introduce the tube themselves. When the condition does not respond to a dietary regimen, improvement is sometimes dramatic as soon as regular lavages have been started. However, the diet should be strictly bland; large meals and coarse food (raw vegetables, raw fruits) should be forbidden. Drug therapy is not necessary. If spasms cause severe pain, small doses of atropine (0.0005 Gm. twice daily) or belladonna may be agreeable. Possible etiologic factors, such as the use of nicotine, defective teeth and foci of infection, should be eliminated.

Chronic Atrophic Gastritis.—In this condition chronic inflammation leads to progressive reduction of the thickness of the gastric mucosa. It comprises 32.3 per cent of all chronic gastritis.

Pathologic Anatomy.—Frequently the transition from superficial to atrophic gastritis may be observed (Fig. 41, *B*). The diagnosis of true atrophic gastritis is made as soon as destruction of the gastric glands is found. Three characteristic features of beginning atrophy may be found separately or together: (1) compression of the isthmus and neck of the gastric glands by inflammatory exudate with formation of retention cysts; (2) cellular infiltration immediately above the muscularis mucosae, gradually destroying the bottom of the glands, and (3) proliferation of the pits.



A



B

Fig. 41.—*A*, gastroscopic view of the transition of chronic superficial gastritis into chronic atrophic gastritis. In the upper portion of the picture chronic superficial gastritis is seen, with layers of adherent mucus and red patches. In the lower portion bloodvessels are visible, lying in a thinned greenish gray mucosa (not demonstrable in the black and white picture). (The photograph is reproduced from a colored picture made by Miss Gladys McHugh.) *B*, microscopic section through the gastric mucosa in a case of severe chronic superficial gastritis, showing extensive infiltration of only the upper layers of the mucosa. Near the left border of the picture a superficial erosion is seen. Examination with higher power magnification showed that the infiltration consisted almost exclusively of plasma cells. (The photograph is published through the courtesy of Dr. M. Ortmayer, who removed the specimen during a cholecystectomy, after having observed the typical picture of superficial gastritis through the gastroscope.)

(1) The superficial edema may become extensive, its plasma cells becoming superabundant. Between the glands the edema is replaced by lymphocystic infiltration.

(2) Sometimes the destruction of the gastric glands starts at the bottom. In addition to the edema and plasma cell infiltration of the surface, there is cellular infiltration immediately above the muscularis mucosae, consisting of small cells and fibroblasts, enveloping and destroying the lower portions of the glands.

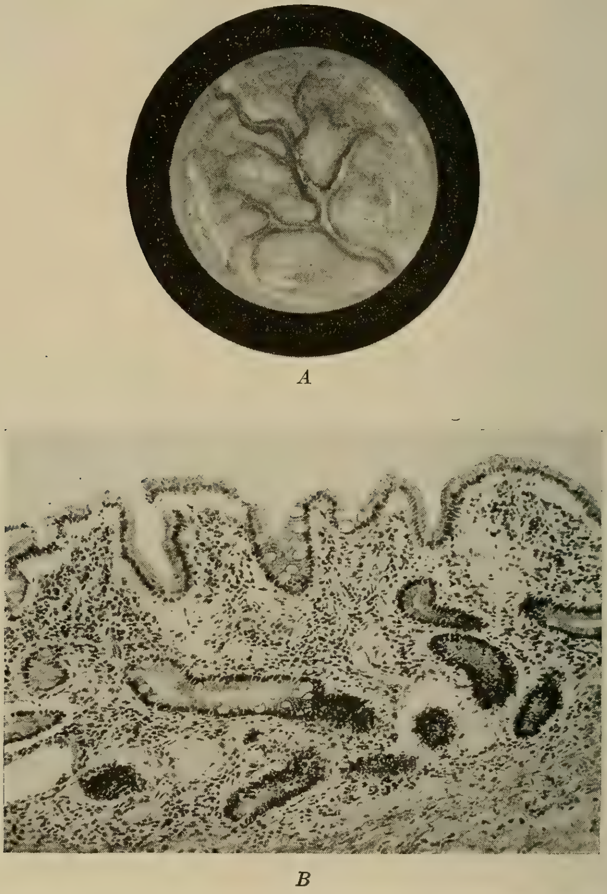


Fig. 42.—*A*, gastroscopic view in a case of chronic atrophic gastritis. The gastric mucosa is so thin that the branching submucosal vessels are clearly visible. (The photograph is reproduced from a picture by Miss Gladys McHugh.) *B*, microscopic section through the gastric mucosa in a case of severe chronic atrophic gastritis. The mucosa has less than a third of its normal thickness. The gastric glands have almost disappeared. Some epithelial cells have been transofrmed into goblet cells; extensive interstitial infiltration is present.

(3) The pits start proliferating at an early stage. They become elongated and corkscrew-like; they grow toward the muscularis mucosae between the glands and may become tortuous and branching.

The chief cells of the gastric glands are the first to disintegrate and to disappear, an important point since the chief cells are the opaque elements of the mucosa and their early disappearance renders the mucosa transparent. The foregoing fact is of significance from the gastroscopic point of view. Later the parietal cells are destroyed also. Edema with plasma cell infiltration may be found when the glands are completely gone. The deep infiltration leads early to the formation of abundant connective tissue, which in the form of characteristic triangular cushions rests on the muscularis mucosae, which in turn may be split up and infiltrated. The remaining body glands undergo a true metaplasia into the pyloric mucus-forming type of glands. The proliferating pits finally dominate the picture and remain present with most severe disease except in the end-stage. Sometimes the epithelium remains normal; in the majority of cases, however, it undergoes a metaplasia into the intestinal type.

Erosions of the epithelium may be found even at the last stage, evidence that even then inflammation is present. The interstitium contains a great variety of cells. Russell bodies are found frequently. Abnormal lymph follicles sometimes become huge and abundant, dominating the whole picture, which then may be called chronic atrophic follicular gastritis. In some cases irregular proliferation of the surface epithelium may be observed, ranging from slight budding to formation of large "pseudopolyps." Edema and exudate together with this proliferation sometimes increase the thickness of the mucosa and may even lead to "tumor-forming" gastritis, although the glands have already disappeared. But finally the thickness decreases and the surface epithelium may almost be resting on the muscularis mucosae. The picture described is the same in uncomplicated atrophic gastritis as well as in atrophic gastritis accompanying benign ulcer, tumor and especially pernicious anemia.

Gastroscopically it is easy to see patches of thin gray or greenish gray mucosa, either sharply limited and depressed or diffusely blending with the surrounding normal or superficially inflamed mucosa. Red or blue bloodvessels of the submuoosa may become visible, with treelike branching and formation of fine anastomoses. It must be emphasized that such bloodvessels will be found only in stomachs in which severe atrophic gastritis can be demonstrated microscopically. Distention of a healthy stomach with the largest possible amount of air will never produce this picture. The gastroscopic differentiation of severe hyperplastic forms of atrophic gastritis from true hypertrophic gastritis (see below) is difficult. In rare cases of dense lymphocytic infiltration the gastroscopic picture may show stiff infiltration, and differentiation from other forms of diffuse infiltration, such as infiltrative carcinoma, Hodgkin's lymphogranuloma and syphilis, may not be possible.

Symptomatology.—Attacks or spells last from some hours to several months. The reason for remission and recurrence is unknown. There are, probably, cases of atrophic gastritis without any gastric symptoms. Symptoms frequently found are: epigastric pressure and fulness, gas and belching, especially immediately after meals. Severe pains occur but rarely. Poor appetite, inability to eat large meals, nausea and vomiting are frequent. Often, however, the patient will consider his gastric symptoms unimportant, but will stress the importance of general symptoms, such as extreme fatigue and weakness, which may become so severe that he becomes incapacitated. Nervousness and irritability are often present. Interesting as far as etiology is concerned is the fact that some patients complain of sore tongue and tingling and numbness in the limbs without blood changes or combined degeneration. The syndrome of epigastric pressure, excessive weakness, poor appetite and nervousness is almost diagnostic, and if sore tongue and tingling or numbness are present, the diagnosis becomes almost certain. Gross hemorrhage has been observed. Severe loss of weight is frequent and may suggest beginning carcinoma. The laboratory findings are not characteristic. In one-third of all cases histamine-negative anacidity will be found, but normal acidity and even hyperacidity may be present. Histamine-proved anacidity is most frequently found in atrophic gastritis, and it may occur in a normal mucosa and with superficial and hypertrophic gastritis also. Lactic acid is sometimes found, which disposes of the old idea that the presence of lactic acid indicates obstruction or stagnation. The cell count of the gastric contents often is increased. There are no typical *x*-ray findings. The gastroscopic picture is absolutely characteristic: thinning of the mucosa is observed; the color becomes gray or greenish gray, and bloodvessels are seen. In severe disease the entire gastric mucosa is gray and thin, and the trees of the branching submucosal bloodvessels sometimes protrude.

Diagnosis.—Atrophic gastritis should be suspected if the mentioned syndrome of epigastric pressure, gas and belching, poor appetite, extreme fatigue, sore tongue and tingling and numbness of the limbs is present. If patients suffering from superficial gastritis become nervous and easily tired, beginning atrophy can be assumed to exist. Atrophic gastritis is always present with pernicious anemia (see p. 178) and sprue.

The differentiation from beginning carcinoma is important. Therefore, even if the mentioned syndrome is present, *x*-ray examination and gastroscopy should not be omitted. In the rare cases in which a gastroscopic differentiation of the different kinds of infiltrative lesions is impossible (see p. 175), diagnostic laparotomy and biopsy of material from the infiltrated stomach wall can be recommended.

If atrophic gastritis has been found, regular blood counts become indispensable, since atrophic gastritis may precede pernicious anemia.

Course and Prognosis.—It was formerly believed that atrophy was an irreparable end-stage of gastritis. However, regeneration of atrophic gastric mucosa is apparently possible. Usually the disease remains unchanged. The patient, though suffering severely and even incapacitated, acquires an attitude of resignation which I consider most dangerous, since it will hide the symptoms of beginning carcinoma. Patients suffering from atrophic gastritis are perhaps threatened to a higher degree by gastric cancer than the average persons, and should be observed carefully and reëxamined at regular intervals.

Observation.—The patient suffering from atrophic gastritis should not be left alone, even if the physician recognizes that he cannot change the underlying anatomic condition. Suggestion, often effected by the mere presence of a good doctor, will help the patient to overcome the worst days. He should be told that regular check-ups every three months are indispensable, but he should not be told that these check-ups still have another purpose than observation of the progress of the disease, namely, the discovery of early carcinoma. The check-up should consist of three special examinations: blood count, *x*-ray study and gastroscopy. The blood count will reveal beginning anemia; by *x*-ray early carcinoma may be discovered, and gastroscopy will show the effect of therapy and may reveal small carcinomas overlooked at *x*-ray examination.

Therapy.—In every case of atrophic gastritis, substitution therapy should be tried, although the prospect is not favorable. If no deficiency state is evident, liver at first and then iron should be given, and finally vitamins (ABD capsules) may be tried. Symptoms may disappear without any therapy, and change of the gastroscopic picture is the only proof of the effectiveness of substitution therapy. Most patients can be treated only symptomatically. Frequent small meals should be given; raw fruits and vegetables should be avoided entirely. Spices should not be eliminated as completely as in the presence of other gastric diseases. Bouillon and carefully roasted soft meat may be recommended. The opinion about the effectiveness of hydrochloric acid is divided. If it is used, large doses in the following form should be given:

	Parts
R Hydrochloric acid (not diluted!)	20.0
Dried pepsin	20.0
Distilled water to make	100.0

Sig.—One tablespoonful in a glass of sugared water to be taken through a glass tube before and during meals.

It is astonishing that patients without anacidity suffering from atrophic gastritis frequently contend that their appetite and condition improve when they take hydrochloric acid. In such cases diluted hydrochloric acid (15 drops in sugared water) may be prescribed. The effect usually is best if the acid is taken before the meals. If gas and belching cause much distress, charcoal (carbo ligni or carbo sanguinis, a teaspoonful in water after meals three times a day) may be tried.

Rest, possibly in bed, after the chief meal is important. Moderate exercise, especially regular walking in fresh air, often is valuable.

Gross hemorrhages should be treated conservatively by bed rest. Surgical measures are indicated only in the rare cases of pyloric obstruction, in which resection should be carried out.

Chronic Hypertrophic Gastritis.—In this condition, infiltration and proliferation of the gastric mucosa lead to its thickening. Gastroscopic observation over a long period has taught that chronic hypertrophic gastritis has no tendency to turn into atrophy. It comprises 41.2 per cent of all chronic gastritis.

Etiology.—Almost nothing is known about the cause of this form. It seems that in rare cases alcoholism is an etiologic factor.

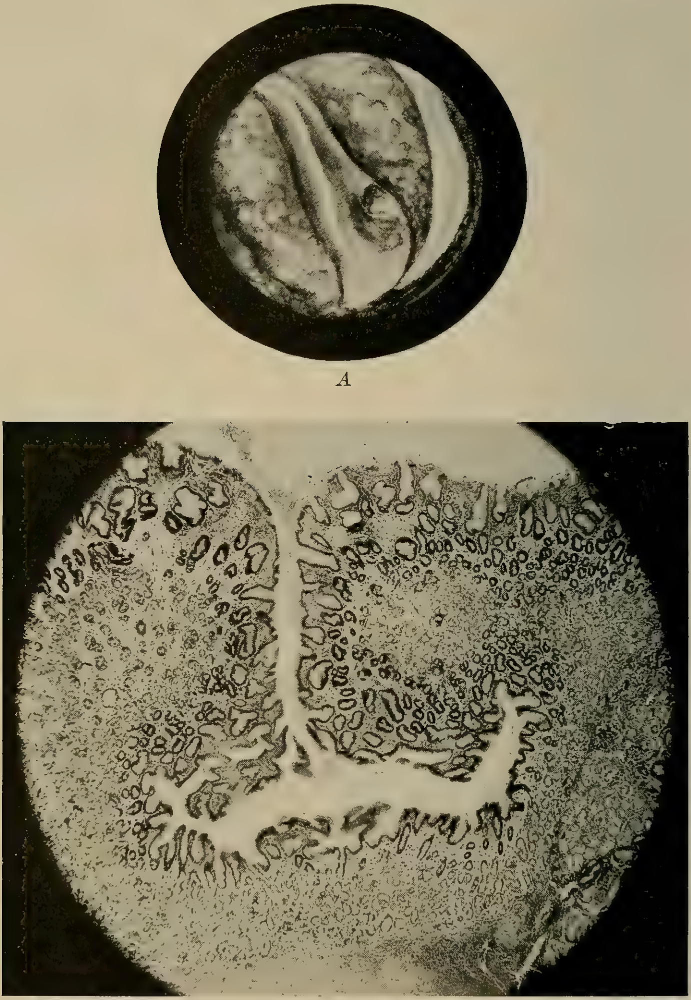
Pathologic Anatomy.—Hypertrophic gastritis cannot be recognized, grossly, in the postmortem specimen except in cases of tumor-simulating proliferation of the mucosa. Some such tumors belong in the atrophic group (*vide supra*). Microscopically three different forms may be distinguished, although grossly at gastroscopic examination the same picture is observed in all of them, namely, (1) hypertrophic interstitial gastritis, (2) hypertrophic proliferative gastritis, (3) hypertrophic glandular gastritis.

(1) In hypertrophic interstitial gastritis may be seen dense lymphocytic infiltration between the long body glands, usually together with enlarged lymph follicles which have no sharp limits.

(2) In hypertrophic proliferative gastritis the length and structure of the body glands are unaltered, but on top of them there is a grotesque proliferation of the surface epithelium, which grows to form irregular large nodes, which double the thickness of the mucosa. Their surface epithelium is most irregular, presenting several rows of nuclei, lack of mucus in the

cells and many mitoses. The interstitium of these nodes contains all kinds of inflammatory cells.

(3) In hypertrophic glandular gastritis inflammatory processes are relatively few, but there is a tremendous over-growth of the glandular apparatus, which may treble the thickness of the mucosa. This may be described as a true hyperplasia, but in most cases signs of inflammation, such as edema, plasma cell infiltration and cysts filled with leukocytes, may be encountered.



A

B

Fig. 43.—*A*, gastroscopic view in a case of chronic hypertrophic ulcerative gastritis. The mucosa between the folds is swollen and nodular. In the central fold is a superficial ulceration surrounded by a red halo. (The photograph is reproduced from a picture by Miss Gladys McHugh.) *B*, microscopic section through the gastric mucosa in a case of severe hypertrophic gastritis. Tremendous proliferation of the mucosa is present, and interstitial infiltration and edema are seen. (This photograph is reproduced through the courtesy of Dr. Ralph Brown.)

In (2) and (3), tumor formation simulating carcinoma may be observed.

The gross appearance is best studied with the gastroscope. In healthy adults the mucosa is glistening and smooth, while in patients with hypertrophic gastritis it has a dull, velvety, loose, spongelike appearance. The area involved later becomes nodular, with a typical "cobble-stone" surface. These changes appear first in the depressions between the folds, but later the folds also become involved and look segmented, caterpillar-like and nodular. Enlargement of the folds is not frequent.

The changes are found most frequently in the body, although sometimes they may be seen in the antrum. Inflammatory small and large mucosal hemorrhages are frequent. From time to time small gray or yellow ulcerations develop; they may disappear ëntirely within a few days.

Symptomatology.—The symptoms are chiefly gastric. Severe ulcer-like pains are present, sometimes not relieved by administration of milk or alkali. The patient states that he has always had a "weak" stomach and had to be careful with his food; that if he were not careful, he would immediately have pains, gas and belching. Delayed pains and night pains are frequent. The appetite may be good or poor; vomiting rarely occurs; the bowel movements usually are regular. Profuse gross hemorrhages occur and may even have a fatal outcome.

Physical examination and laboratory tests give essentially negative results, although occult blood may be found in the stools. The x-ray gives a characteristic picture in the extremely rare cases of "corncob-relief picture," caused by the presence of inflammatory nodes. Stiffness of the folds on palpation at fluoroscopy may be suggestive, although the significance of this symptom is not entirely clear. X-ray demonstration of thick folds, often considered diagnostic by European workers, is of no diagnostic value. The gastroscopic picture is characteristic.

Diagnosis.—If in a patient having ulcer symptoms no ulcer is found at x-ray examination, chronic hypertrophic gastritis may be suspected. However, the differentiation from chronic superficial gastritis, psychoneurosis and even sometimes gastric cancer is possible only gastroscopically.

Course and Prognosis.—Chronic hypertrophic gastritis has no tendency to heal completely, in contrast to superficial gastritis. If the patient is reëxamined during pain-free intervals, areas of hypertrophy still will be found. At the time of an attack of pains, superficial ulcerations usually are present. Life is not threatened except in rare cases of gross hemorrhage.

Therapy.—Such a bland diet should be prescribed that the patient is able to follow it through his lifetime. At the time of an acute attack of pains or of gross hemorrhage, bed rest is indicated. Pains are relieved by hot applications; administration of alkalis is sometimes helpful. High voltage x-ray therapy most definitely influences hypertrophic gastritis, and may change the swollen gastric mucosa to a normal one. However, the late results are not well known; sometimes severe atrophy develops; therefore, this type of therapy can be recommended only for the most desperate lesions. Surgical intervention is not indicated, especially not in cases of repeated gross hemorrhage. The bleeding often continues from the mucosa of the resected stomach.

Complications and Sequelae of Chronic Gastritis.—**Concomitant Inflammation of Intestine and Biliary Tracts.**—Diarrhea is not a symptom of chronic gastritis. If it is noted, concomitant enteritis should be the diagnosis. Probably chronic inflammation of the entire gastrointestinal tract is not rare.

Coincidence of gastritis and cholangitis is frequent, and it seems that either the stomach or the gallbladder can be affected primarily, although the possibility exists that there is no connection between the two. The following sequence of events has been observed: primary acute simple exogenous gastritis; development of chronic superficial gastritis; involvement of the biliary tracts; icterus, and death from ascending cholangitis.

Nothing is known about the relation of gastritis to esophagitis and pancreatitis.

European workers, especially Konjetzny and Hurst, have called chronic gastritis the soil and the exclusive cause for pernicious anemia, chronic gastric ulcer and gastric carcinoma. I can agree with this important conception only as far as it concerns a certain number of gastric carcinomas.

Relation of Chronic Gastritis to Pernicious Anemia.—There is no case of pernicious anemia without outspoken diffuse alterations of the gastric mucosa. Usually patchy atrophic gastritis or complete atrophy is seen, but sometimes there is superficial gastritis. The opinion that chronic gastritis destroys the Brunner glands, which are said to be the source of the "antianemic factor," and by this means produces pernicious anemia, is hardly tenable. As I have mentioned, liver therapy may lead to an apparent cure of this type of atrophic gastritis; therefore, it is more likely that lack of the antianemic factor leads to a degeneration of the surface epithelium, with superimposed inflammation and secondary atrophy. The gastric disease then would develop parallel to the blood changes, the changes of the nervous system (combined degeneration) and the glossitis and pharyngitis, so often observed with pernicious anemia. Some links of this chain of symptoms may be missed entirely; atrophic gastritis may be present without any blood changes.

Relation of Chronic Gastritis to Chronic Gastroduodenal Ulcer.—In 41 per cent of all cases of gastric ulcer some kind of gastritis is found gastroscopically, either surrounding the ulcer as a small border of swelling or involving the entire gastric mucosa. The theory of the gastritic origin of the ulcer (see Chaptër IX, p. 189) is based on the experience that in resected specimens of gastric and duodenal ulcer severe gastritis, with formation of grossly visible acute ulcerations, often is seen (Konjetzny). It seems likely now that these lesions were artefacts caused by the act of resection; *i. e.*, the action of hydrochloric acid on a gastric mucosa the blood supply of which has been interrupted rapidly effects ulcerative gastritis. Therefore, the frequent gastritis of the ulcerous stomach should be considered secondary to the ulcer.

Relation of Chronic Gastritis to Gastric Carcinoma.—The old assumption that gastric carcinoma develops only in persons who previously had an entirely healthy stomach is not correct. On the contrary, a long story of epigastric distress is found in about one-third of all cases. Histamine-proved anacidity may precede the development of gastric carcinoma by ten years or more. Modern statistics seem to prove that patients suffering from chronic gastritis are three times more prone to gastric carcinoma than healthy persons. Morphologic studies by Guiss and Stewart do not support this theory, but in spite of this I believe that some carcinomas develop on the soil of chronic gastritis, and if this does happen, then careful examination of patients with atrophic gastritis would open an avenue for the incidental discovery of minimal carcinomas—genuine "early" carcinomas—and for their cure by early gastric operation. This has been done, and the possibility makes it imperative: (1) to diagnose and treat thoroughly chronic superficial gastritis in order to prevent a precancerous atrophic gastritis, (2) to diagnose and treat thoroughly the precancerous atrophic gastritis, (3) to make regular careful *x*-ray and, if possible, gastroscopic observations of patients suffering from this condition.

Appendix

Diffuse, Not Strictly Inflammatory Diseases of the Gastric Mucosa.—Atrophy of the gastric mucosa usually is a product of inflammation, rather than being strictly degenerative.

Whether noninflammatory hypertrophy exists is unknown. There are two condictions which should not be classified as inflammation: (*a*) localized gastric purpura and (*b*) allergic manifestations of the gastric mucosa.

Localized Gastric Purpura.—In some patients suffering from epigastric pain gastroscopic examination shows the same picture as that of generalized hemorrhagic diathesis, namely, mucosal hemorrhages scattered over an entirely normal, noninflamed mucosa. These hemorrhages have been seen microscopically by Robertson. Concomitant occurrence of deep-lying pigment spots and typical hemorrhagic erosions in a non-inflamed mucosa prove that these hemorrhages are not artefacts. Since this condition is found in 2 to 5 per cent of all patients examined with the gastroscope, but in 44 per cent of all patients with gastric ulcer, a casual connection between these two lesions may exist, and the hemorrhagic erosion may represent the acute stage of the chronic gastric ulcer. Localized gastric purpura may be suspected in patients with symptoms but without demonstrable ulcer. The therapy should be identical with that of gastric ulcer (see p. 217).

Gastric Allergy.—Mucosal changes due to gastric allergy have been observed thus far only by René Chevallier. He described tremendous transient edematous swelling of gastric folds in allergic patients. At *x*-ray examination this swelling even suggested tumor formation. Whether or not these phenomena should be called inflammation could be decided only by microscopic examination.

Gastroscopy.—Gastroscopy, the direct inspection of the gastric mucosa, is now well established. *X*-ray study and gastroscopy complement each other ideally. It seems that the safe flexible gastroscope will be used increasingly in the daily routine examination of patients suffering from abdominal distress.

Attempts at looking into the stomach were made as early as 1868 by the use of open tubes (Kussmaul, 1868; Chevalier Jackson, 1907); with flexible tubes which had to be straightened after their introduction into the stomach (Kuttner, 1897; Sussmann, 1911), and with straight rigid tubes (Miculicz, 1881; Loening-Stieda, 1908; Elsner, 1911; Schindler, 1922); but only after the invention of the safe flexible gastroscope in 1932 was the procedure generally adopted.

The chief obstacle to the further development and wider use of such inspection consists in its confusion with open tube procedures, such as esophagoscopy. Open tubes are often disagreeable for the patient, and they may become dangerous. The flexible gastroscope, however, can be compared only with a flexible stomach tube, remaining flexible and bent during the entire examination (Fig. 44). A rubber finger leads the instrument safely through the esophagus and along the posterior wall of the stomach. An electric lamp illuminates the gastric wall. The objective collects a cone of rays coming from the gastric wall and forms a small picture, which then is transmitted through the lens system of the flexible portion. The lenses of this flexible portion are arranged in such a manner that the picture remains entirely sharp, however, this portion may be bent, up to an angle of 34 degrees. The flexible portion remains flexible during the entire examination. The rigid portion permits the direction of the tip in the interior of the stomach. The examiner observes the picture through the eye piece (*ocular*). The air balloon permits inflation of the stomach with air for the distention necessary for inspection. The cable connects the lamp with an electric current.

After careful local anesthetization of the pharynx, this instrument is introduced like a simple Ewald stomach tube, with the patient on the left side. The patient should not have taken anything by mouth for about twelve hours before the examination, but he does not need hospitalization. He may work immediately after the examination, and usually he experiences so little discomfort that he does not object to repeated examinations.

The *contraindications* for this procedure are essentially the same as for the introduction of a simple stomach tube, but they may be listed here again: Gastroscopy should not be carried out in the presence of (1) obstruction of the esophagus or of the cardia (this most important contraindication should be ruled out by introduction of a thick Ewald tube immediately before the gastroscopic examination), (2) aneurysm of the aorta, (3) corrosive and phlegmonous acute gastritis and (4) suspected esophageal varices (especially in liver cirrhosis). Relative contraindications are angina pectoris, dyspnea, severe kyphoscoliosis of the spine, cardiospasm, esophageal diverticulum and psychoses. Noncoöperation of the patient will render gastroscopy unsuccessful.

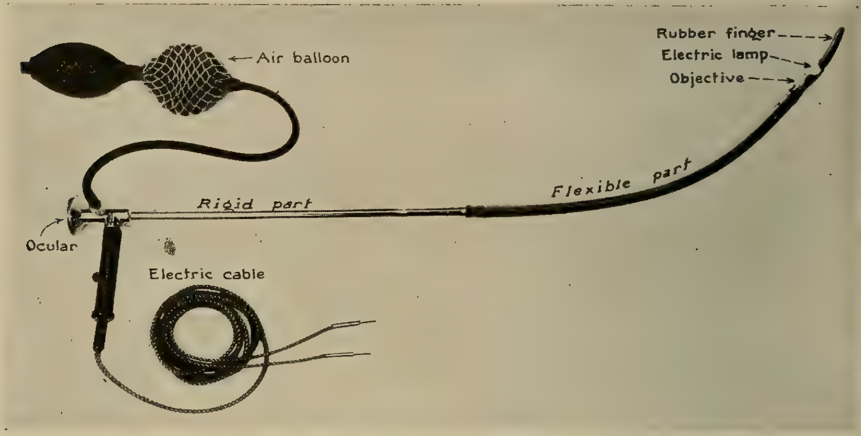


Fig. 44.—The flexible Wolf-Schindler gastroscope.

The *indications* are manifold, and in the future gastroscopy will be carried out in most cases of abdominal distress. After a complete clinical check-up and careful x-ray examination, gastroscopy should be carried out if:

(1) in a patient suffering from abdominal distress no organic disease is found by x-ray. (Extensive statistical studies have shown that localized lesions, such as beginning carcinoma and even some ulcers, which have escaped discovery at x-ray examination, may be found by gastroscopy. Organic lesions not accessible to x-ray, especially gastritis, may be discovered at gastroscopy.)

(2) at x-ray examination a gastric ulcer in a patient over 35 years of age has been found. (The fact that at gastroscopy sometimes the differential diagnosis between benign and malignant ulcer is much easier than at the inspection of the gross section is readily explained by the fact that the circulating blood makes the gastroscopic picture exceedingly colorful, and reveals much detail of the relief.)

(3) at x-ray examination a lesion is found, the true nature of which cannot be diagnosed immediately. (At gastroscopy the nature of a pyloric obstruction, for instance, may be recognized at once.)

(4) unexplained gross hemorrhage has occurred.

(5) after gastric operation, the patient continues to have gastric symptoms or has new or recurrent symptoms.

(6) a malignant tumor has been found by x-ray (in order to determine its operability and its gross type; in such a case gastroscopy is unnecessary if the impossibility of an operation has been proved by the clinical or x-ray picture).

(7) a benign tumor has been diagnosed at x-ray examination. (It might be a malignant one.)

(8) the healing process of a benign gastric ulcer is to be watched or if operation for gastric or duodenal ulcer is considered.

(9) previous gastroscopy has shown one of the so-called precancerous conditions. (In such a case repeated x-ray and gastroscopic examinations become necessary to discover early carcinoma (see p. 269.)

It is evident that gastroscopy does not belong in the hands of a few experts only, but should be mastered by the specialist in internal disease and especially by the gastroenterologist, and used frequently. Each general hospital should have facilities for gastroscopic examination. The orientation in the large cavity of the stomach and the correct interpretation of the picture seen are difficult, and demand special, thorough training.

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CHAPTER IX

PEPTIC ULCER

DESCRIPTION

Esophageal, gastric, duodenal and jejunal (anastomotic) ulcer will be considered together in this chapter under the heading of peptic ulcer, because the lesions are essentially the same. The term "peptic" has been sanctioned by usage, but it over-emphasizes the role of pepsin in the pathogenesis of ulcer. Other adjectives, such as digestive, corrosive, eroding, simple, round, perforating, acid, etc., have not been generally adopted.

Pathology.—**Location.**—Peptic ulcer occurs only in those portions of the digestive tract exposed to the action of acid gastric juice, *i. e.*, the lower portion of the esophagus, the stomach and the first portion of the duodenum. After gastroduodenostomy, gastrojejunostomy or gastroileostomy, ulcers may form in those portions of the bowel adjacent to the stoma. Peptic ulcer in Meckel's diverticulum is associated with heterotopic gastric mucosa in the diverticulum. Taylor[119] reported a case of chronic peptic ulcer of the ileum associated with a curious mucosal mass 10 inches from the ileocecal valve and composed of glands of the type found in the fundus of the stomach, with numerous oxyntic cells. In the stomach the lesion occurs almost exclusively along the so-called *Magenstrasse.* Rivers and Dry[101] found in the files of the Mayo Clinic only 4 cases of ulcer of the greater curvature, and Matthews,[76] in reviewing the literature in 1935, was able to collect only 22 cases. Peptic ulcer may occur in the pylorus itself or adjacent to it (pre- or postpyloric). Most duodenal ulcers occur in the first portion; a few occur in the upper part of the second portion.[73]

Distribution.—Peptic ulcer occurs in all regions of the earth and among all peoples, although a low incidence has been reported in certain sections of northern India[72] and among the native Malays of Java and Sumatra.[17] In view of the wide distribution of the lesion in all other sections and peoples of the world, final judgment regarding its scarcity in these regions may justifiably be withheld until further studies have been made. Occupation does not seem to be a factor; the disease occurs in persons in all walks of life.

Peptic Ulcer in Animals.—In certain mammals such as the dog, spontaneous peptic ulcer is rare, but it is common in rabbits. Gastric ulcers not infrequently develop in calves at the time of weaning, and the veterinarians have learned that the proper treatment is a milk diet. Schlotthauer[113] gave an interesting discussion of peptic ulcer among mammals, referred to an "epizoötic of spontaneous perforating gastric ulcers in ranch foxes" reported by Shillinger[116] and described the clinical history as well as the autopsy findings in a horse which had two gastric ulcers, one of which perforated. Apparently nothing is known regarding the occurrence of ulcer in animals other than mammals.

Incidence.—The exact incidence of peptic ulcer is unknown. Autopsy and *x*-ray study have shown that from 10 to 12 per cent of all persons suffer at some time in their lives from a chronic gastric or duodenal ulcer.[40]

In the earlier postmortem studies gastric ulcers and scars were much more frequently observed than duodenal. In recent years, however, the figures have been reversed, presumably because of more careful study of the duodenum.

Statistics on the sex incidence are also somewhat variable, although there is general agreement on the greater prevalence of duodenal ulcer in the male, in the ratio of about 4 to 1. For gastric ulcer the male to female ratio is 3 or 4 to 1.

Peptic ulcer occurs at all ages. In the newborn, acute ulcers are not uncommon, but they are not recognized clinically unless they produce melaena neonatorum or perforate with resultant peritonitis. Both acute and chronic lesions occur in all decades of life, but they are rarely diagnosed in the first decade unless the complications of acute perforation or massive hemorrhage are present. The average age of onset is five to ten years earlier for duodenal than for gastric ulcer.

There is a general tendency to emphasize the familial incidence of ulcer. Striking examples are occasionally encountered, such as the 6 cases in one family reported by Turner and Lattuf.[122] Hurst cited certain evidence, such as the studies of Bauer and Aschner,[10] to show that the incidence is greater than might be expected on the basis of coincidence, but conclusive proof is lacking.

Constitutional Type.—The lean, thin person is said to be the ulcer "type,"[35] but the lesion is not infrequently seen in short, stocky, obese patients. The constitutional type is of no real clinical significance in the ulcer problem.

Multiple Lesions.—Although ulcers are usually single, not infrequently they are multiple. They occur in both stomach and duodenum (15 per cent, according to Carman[24]) or more often in either the stomach or the duodenum, where they are well known as the "kissing ulcers" of the anterior and posterior wall. The gastroscopist frequently sees two or more gastric ulcers when the roentgenologist sees only one.

Description.—An ulcer is a circumscribed area of less of tissue, from 5 to 25 millimeters in diameter, although it may be only 2 or 3 millimeters in diameter or as much as 40 to 60 millimeters. It differs by definition from an erosion in that it involves not only the mucosa but the muscularis mucosae. Figure 45, taken from Konjetzny,[66] illustrates in one section the transition from an erosion limited to the superficial layers of the mucosa, as in *A* and *E*, to an acute ulcer in which the muscularis mucosae has been penetrated and the submucosa involved, as in *C* and *D*. Peptic ulcer is a penetrating process beginning in the mucosa and invading the deeper layers of the gastric wall, perhaps perforating the wall completely—leading to acute perforation—or penetrating a large bloodvessel with resultant massive hemorrhage. All ulcers are in fact "penetrating" ulcers.

Acute and chronic ulcers differ chiefly in respect to the quantity of granulation and fibrous tissue present. Most ulcers represent varying stages of chronicity. The lesion usually has a sharp, cleancut border and is surrounded by normal or slightly inflamed mucosa. In very acute ulcers the border may be flat, but usually it is elevated and rounded, owing to extensive edema of the submucosa. Occasionally the elevated border is due to extensive fibrous tissue proliferation. The floor of a peptic ulcer is clean. It is covered by a thin layer of fibrinopurulent exudate, beneath which there is a narrow zone of fibrinoid necrosis. The base beneath consists of granulation and fibrous tissue, with some muscularis. In chronic ulcer the muscular layer is usually completely interrupted by fibrous tissue, and the bloodvessels are thrombosed. Not infrequently the base consists of the capsule of the pancreas or of the liver. The lesion may invade the substance of these or other structures. Evidence of extension of the ulceration and of healing usually are to be found at the same time. Apparently the ulcerative and reparative processes alternately gain ascendancy. Ulceration may progress in one part of a lesion while healing is progressing in another. If ulceration is dominant, perforation or hemorrhage ensues; if healing is dominant, scar tissue proliferates, and a thin layer of mucosal cells grows across the defect and gradually becomes transformed into cuboidal and then columnar epithelium, atypical mucosa and finally normal mucosa, and the ulcer heals (Figs. 46 and 47). The process is usually a continued struggle between the two tendencies, ulceration and healing, first one and then the other being dominant. The "life history" of an ulcer is thus characterized by remissions and exacerbations. In the remission the lesion may heal completely or only partially. Exacerbation may be due to reactivation or extension of the lesion or to the development of a new ulcer at a different site. If the initial ulcer is an acute one, even though it is large, and if it heals promptly, there may be almost no scar. If, on the other hand, the process is chronic, with continued fibrous tissue proliferation and yet without complete healing, cicatricial deformities ensue. In the stomach, because of its large size, these are usually not noticed, but they may produce hour-glass contracture. In the duodenum, however, the deformity is more easily seen anatomically and roentgenologically.

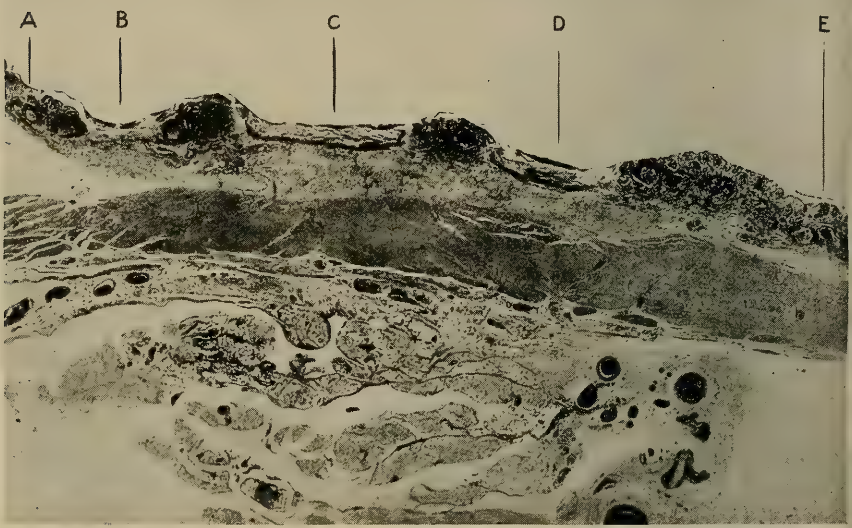

Fig. 45.—Superficial erosions (*A* and *E*); a deep erosion (*B*) with inflammatory infiltration of the muscularis mucosae (transition to acute ulcer), and two acute ulcers (*C* and *D*), extending through the muscularis mucosae. (Photograph, courtesy of Dr. G. E. Konjetzny.[66])

Curling's Ulcer.—In 1842 Curling collected a series of cases of gastroduodenal ulceration following extensive burns of the skin. Credit for the first report of this condition is usually given to Long, but Harkins[53] in a very complete and comprehensive review of the subject gave the credit to Swan (1823). The lesion is usually found at autopsy. Harkins collected 94 such cases in the literature and 13 cases in which recovery occurred. Two reports of ulceration following freezing were found. Curling's ulcer

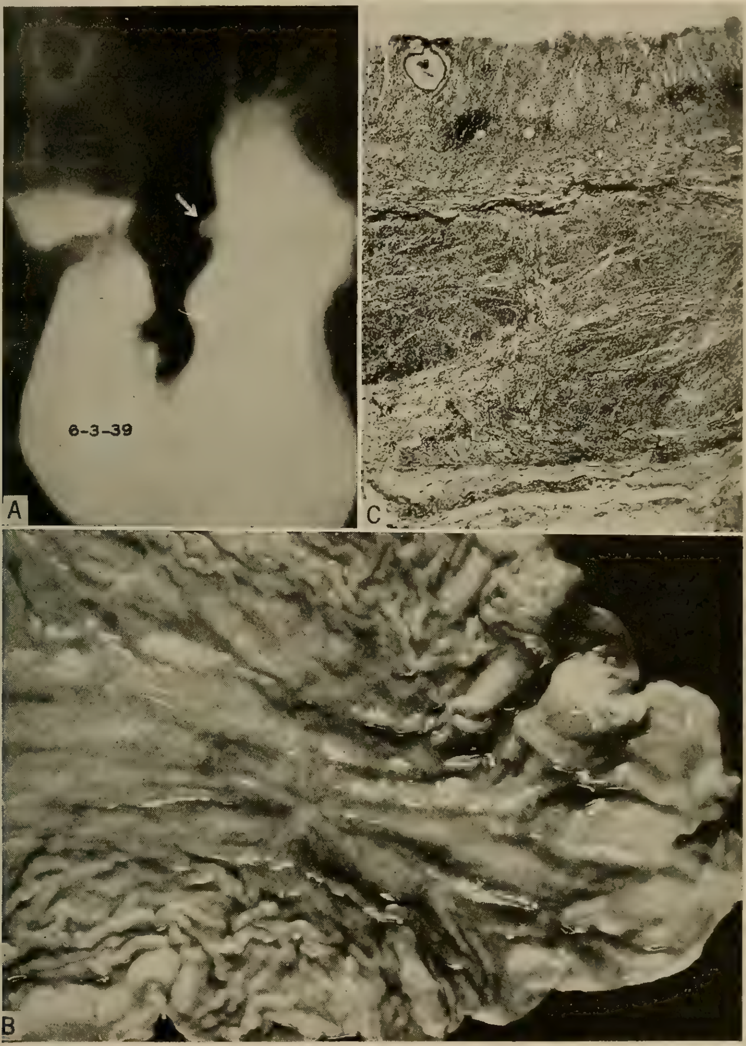

Fig. 46.—The patient, a man aged sixty-three years, entered the hospital June 1 and died July 26, 1939, of syphilitic aortitis, cardiac decompensation (aortic regurgitation) and terminal pneumonia (autopsy). Epigastric distress compatible with ulcer had been present for about a year. The penetrating gastric ulcer found roentgenologically on June 3, 1939, is well shown in *A*. On June 29, 1939, after twenty-six days of ulcer management, the roentgenologist was unable to find any evidence of ulcer. At autopsy, July 27, the scar of the healed ulcer was found (*B*). In the photomicrograph of the lesion (*C*) the regenerated mucosa and the scar are shown.

occurs in both sexes at all ages in either the stomach or the duodenum or both, but usually near the pylorus; it may be single or multiple. The symptoms appear within a few days after the burn. Hemorrhage is twice as frequent as acute perforation; both are common. Nausea and vomiting,

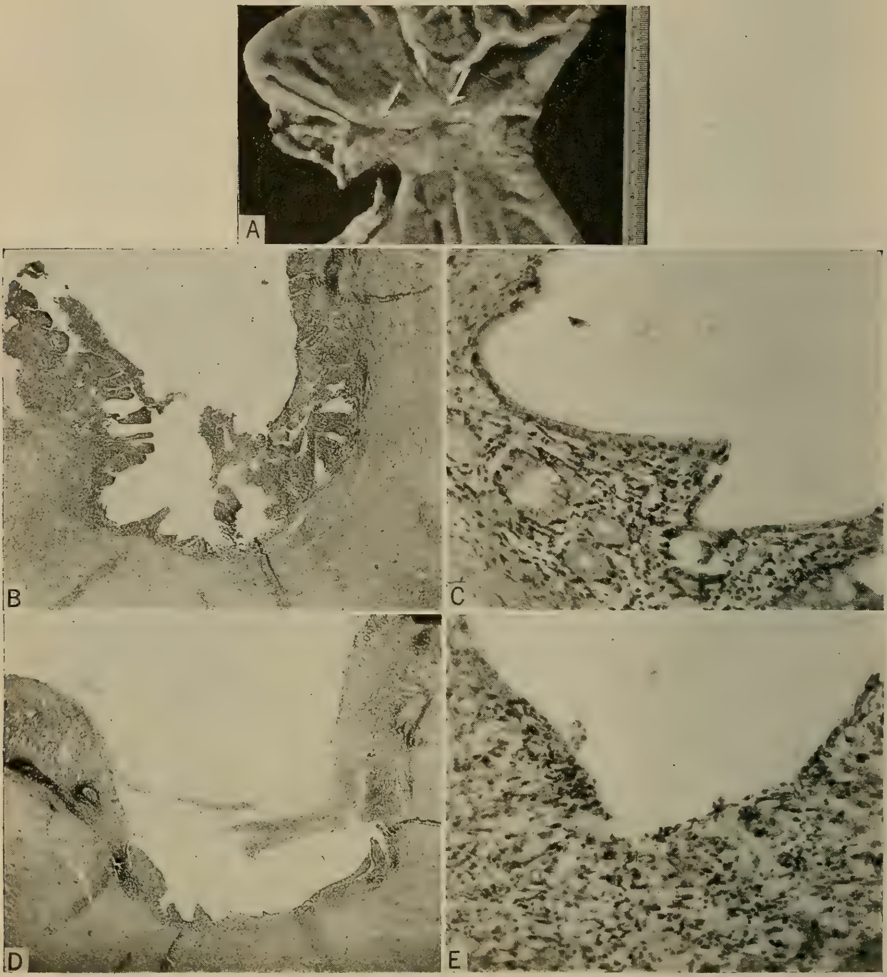

Fig. 47.—The patient, a man aged forty-eight years, entered the hospital June 7, 1939, because of burning epigastric distress of the ulcer type, recurrent for ten years, nasuea and vomiting daily for one month and a 13 pound loss of weight in two years. Marked alkalosis was present on admission (vomiting and alkali ingestion at home). Histamine tests (0.5 mg.) June 15, 18, 24 and 25 all failed to disclose free acidity (explanation unknown—there was fluoroscopic verification of the gastric location of the tip of tube in one experiment), but on June 30 abundant acid secretion was found, reaching 52 units after 0.5 mg. of histamine and 76 after 1 mg. (pH, 1.6). *X*-ray examination disclosed gastric retention and narrowing of the antrum. Gastroscopically an extensive hypertrophic gastritis was seen, with a superficial ulceration at the angulus. After ten days of management, the gastritis was found to have improved spectacularly, and the ulceration at the angulus was very shallow and tiny. Gastric retention was marked, and hence operation was advised. Two healed or healing ulcers were found as shown in the resected specimen (*A*) with photomicrographs of the healed ulcer at the pylorus (away from ruler, *B* and *C*) and of the healing ulcer (near ruler, *D* and *E*). The different phases of the healing process are evident. Note particularly the thin (one cell) layer of mucosal cells in *E*.

epigastric pain and tenderness may be present. If the patient recovers from the burn, the ulcer may become chronic.

Etiology and Pathogenesis.—Theories of the cause of ulcer formation have been legion.[124] The subject may be considered under the following headings:

1. **Bacterial Inflammation.**—The concept of a bacterial cause for ulcer is supported by the frequency with which acute lesions are found after death from acute infectious diseases. Such acute ulcers, however, are found also after death from other causes, such as Addison's disease or essential hypertension. Numerous organisms have been cultured from the floor of human ulcers, but no single bacterium has been found constantly associated with the process. Furthermore, the histologic picture is more suggestive of nonbacterial or chemical inflammation than of bacterial inflammation. The bacterial theory was greatly promoted by the work of Rosenow. Final experimental proof of the role of bacteria in the causation of ulcer has not been adduced,[62] and the clinical evidence is inconclusive. Ulcers may arise during or subsequent to an acute febrile illness, such as a streptococcic sore throat, but such a sequence is uncommon. Although foci of infection were once thought to be of etiologic significance, ulcer is frequently seen in the absence of demonstrable foci. Specific ulcers, such as the tuberculous and the syphilitic, are, of course, due to specific microorganisms, but the typical chronic peptic ulcer is apparently not of bacterial origin.

2. **Nonbacterial Inflammation.**—The theory of nonbacterial inflammation as a cause, particularly the version espoused by Konjetzny, is now prominent, especially in Germany. Its basis is the demonstration by certain pathologists (Stoerk, Moszkowicz, Puhl, Konjetzny and others) of gross and histologic evidence that a certain type of ulcerative inflammation of the lesser curvature, antrum and duodenal bulb, a so-called antral gastritis, is invariably present with ulcer. The same process has been found without the gross "round ulcer of Cruveilhier" and has apparently been responsible at times for the so-called *Ulkuskrankheit ohne Ulkus*. The epigastric distress typical of ulcer as well as massive hemorrhage have been seen in patients whose stomachs after subtotal resection disclosed only this type of gastritis. Complete histologic evidence of the transition from an acute erosion to an acute ulcer has been obtained (Fig. 45). A chronic ulcer obviously arises from an acute ulcer. The cause of the gastritis is admittedly unknown. One of the further difficulties with the gastritic theory of the origin of ulcer is the fact that gastroscopists such as Schindler[111] usually report the mucosa about the ulcer to be normal and cannot confirm the finding of gastritis in the antrum. Schindler, Necheles and Gold,[112] in fact, contended that the "gastritis" of Konjetzny is an artefact produced by interference with the blood supply to the stomach and acid digestion during the brief period required for resection. However, the validity of the demonstration of the transitions from acute erosions to acute and chronic ulcer remains. If Konjetzny's concept stands the test of time, the cause of the gastritis will remain to be determined.

3. **Trauma.**—The traumatic theory of the cause of ulcer needs to be considered only rarely, when the onset of symptoms occurs shortly after a significant blow to the upper part of the abdomen. It is, of course, difficult to be certain that the relation in such instances is not mere coincidence,

but a sufficient number of cases have been described to suggest a direct cause and effect relation.[41]

4. **Infarction.**—The infarctive theory of Virchow was based on the crater-like appearance of the lesion, on the frequent demonstration at autopsy of defects in the gastric wall giving the appearance of an infarct digested out by the gastric juice and on the demonstration of thrombosed vessels in the base of the ulcer. The thrombosed vessels are now known to be the *result* rather than the *cause* of the lesion, for they may not be present in the base of acute ulcers, and approximately 90 per cent of the blood supply to the stomach may be interrupted without significant injury to the mucosa. The infarctive theory is, therefore, no longer tenable.

5. **Chemical Inflammation.**—The chemical theory of ulcer genesis has taken many forms. Hyperacidity has generally been considered to be present with ulcer. It is now apparent, however, that the gastric secretion in patients with ulcer does not differ quantitatively or qualitatively, so far as differences may be measured by the usual test procedures, from normal. Furthermore, the gastric secretion appears to be the same in periods of remission as in periods of exacerbation. The physiologic problem remains, however, of why the stomach itself is not digested by the gastric juice. Claude Bernard showed that the living frog's leg is digested by gastric juice. Various theories such as that of a pepsin-antipepsin balance have been suggested, but none seems very satisfactory. Dragstedt found that the concentration of acid is of greater importance in the digestion of living tissue by gastric juice than is the pepsin content. There is some evidence[9] that the cells of the gastric and duodenal mucosa are normally protected from digestion by the thin layer of mucus with which they are covered, and that in the presence of ulcer the secretion of mucus is deficient. Büchner, Seibert and Molloy,[21] on the basis of histologic evidence and rat experiments, expressed the belief that the gastritis and duodenitis of Konjetzny are of peptic origin—a concept Konjetzny vigorously rejected. Many of the details of the process of ulcer formation are still obscure, but there can be little doubt that "peptic ulcer" is dependent on the presence of acid gastric juice and that the process is due to a failure of the normal mechanism whereby the mucosa is protected from the digestive action of the fluid with which it is bathed. The evidence may be briefly reviewed:

(1) Peptic ulcer occurs only in those portions of the digestive tract exposed to the action of acid gastric juice. (2) Chronic peptic ulcer does not occur in the complete absence of acid gastric juice.[93] Approximately 10 per cent of the population is achlorhydric and is not susceptible to ulcer. The failure of various authors[63] to find active chronic ulcer in the presence of pernicious anemia is striking and significant. Acute superficial lesions can apparently occur, however, with achlorhydria,[103] but they heal rapidly and do not become chronic. The experimental evidence on the importance of acid gastric juice is equally conclusive. Mann and Williamson produced duodenal ulcer in dogs regularly by transplanting the common bile and the pancreatic duct into the terminal part of the ileum, and jejunal ulcer by draining the duodenum into the ileum, thus allowing the unneutralized acid chyme to be discharged into the jejunum. Matthews and Dragstedt anastomosed a Pavlov pouch to a blind loop of intestine, thereby allowing the gastric juice to flow continuously over the intestinal mucosa, with the result that ulcers regularly developed in the bowel.

These ulcers begin in the mucosa and gradually penetrate the wall. They perforate and bleed just as ulcers in human beings do. They are *penetrating* lesions apparently identical with those of human beings. If protected from the further action of acid gastric juice, they heal. Mechanical factors were found to be important in determining the site of the ulcer and the rate of its development, but "it should again be emphasized that chronic peptic ulcer has only been produced consistently experimentally by methods which prevent the neutralization, dilution or buffering of the gastric content as it passes from the stomach."[74] Mann also produced experimental ulcer by the daily administration of hydrochloric acid by means of a continuous drip into the stomach. More recently Code, Varco, Wangensteen and their co-workers[28] have shown that typical chronic peptic ulcers may be produced regularly in the dog and other animals as a result of the continued gastric hypersecretion induced by the injection of a slowly absorbable mixture of histamine and beeswax. The clinical and experimental evidence confirms the dictum of Schwarz,[115] enunciated in 1910, "No acid—no ulcer," but the question as to why ulcer occurs in some persons with acid gastric juice and not in others with equally acid gastric juice remains unanswered. It is tempting to relate the lesion to the excessive continued gastric secretion occurring during the night in patients with ulcer, but it is not as yet determined how constant this state of affairs is and whether it precedes or follows the formation of the ulcer.[56] Bloomfield[15] concluded that "certain people, usually with duodenal ulcer, secrete under basal conditions a larger volume of gastric juice of higher acidity than is ever attained in normal asymptomatic individuals."

Pathogenetically the Curling ulcer seems to be analogous to the ulcers produced by Code, Varco, Wangensteen and others.[28] Necheles and Olson[82] found experimentally that after extensive burns there is a "rapid and considerable increase in gastric secretion, amounting to several hundred percent." Code and Macdonald[27] found a marked rise in the activity of the blood following burns. Rosenthal[104] found this histamine-like substance to differ from histamine in various respects, such as heat lability. All evidence strongly suggests, however, that Curling's ulcer is a result of excessive gastric secretion induced by the presence in the blood of histamine or a histamine-like substance.

6. **Nerve Lesions.**—The neurogenic theory of peptic ulcer was beautifully discussed by Harvey Cushing[33] in 1932 and by others.[30] Cushing reviewed the literature and presented his experience with acute erosions and ulcers of the esophagus, stomach and duodenum associated with intracranial lesions, including primary and secondary neoplasm and malignant hypertension. He then summarized the pertinent experimental evidence and concluded that the evidence strongly suggests

> . . . the presence in the diencephalon of a parasympathetic center. From this center, apparently tuberal in situation, fiber tracts pass backward to relay with the cranial-autonomic stations of midbrain and medulla of which the vagal nucleus is by far the most important because of its influence upon the activity of the lungs, heart and upper alimentary canal.
>
> Experimental lesions anywhere in the intracranial course of these fiber tracts from anterior hypothalamus to vagus center, presumably from parasympathetic stimulation (or possibly from vagal release due to sympathetic paralysis) are prone to cause gastric erosions, perforations or ulcers. Intracranial injuries and diseases affecting these same basilar regions of the brain are known to be accompanied by

> ulcerative lesions of the upper alimentary canal. It is reasonable to believe, therefore, that the perforations following the cerebellar operations forming the basis of this study were produced in like fashion by an irritative disturbance either of fiber tracts or vagal centers in the brain stem . . .
>
> Stimulation of the postulated parasympathetic center by intraventricular injections of pilocarpine or pituitrin cause, in man, an increase in gastric motility, hypertonus and hypersecretion leading to retching and vomiting which ultimately contain occult blood. The same effects, associated with observable patches of hyperemia of the gastric mucous membrane, have been shown to follow direct electrical stimulation of the tuber cinereum in animals . . .
>
> The parasympathetic apparatus, in all probability, under normal conditions is . . . strongly affected by cortical or psychic (Pavlov) influences. However this may be, direct stimulation of the tuber or of its descending fiber tracts, or what theoretically amounts to the same thing, a functional release of the vagus from paralysis of the antagonistic sympathetic fibers, leads to hypersecretion, hyperchlorhydria, hypermotility and hypertonicity, especially marked in the pyloric segment. By the spasmodic contractions of the musculature, possibly supplemented by accompanying local spasms of the terminal blood vessels, small areas of ischemia or hemorrhagic infarction are produced, leaving the overlying mucosa exposed to the digestive effects of its own hyperacid juices.

The stage is thus set for the entrance of the psychiatrist and the psyche. There is, indeed, a rather general tendency to associate ulcer with worry, nervous strain or nervous instability. Alexander[3] and his associates have carried out psychoanalytic studies in a rather small number of cases and "consider as a well established finding the significance of strong receptive dependent wishes which are rejected by the conscious personality." They were unable, however, to state "how commonly psychogenic factors are involved in the etiology of peptic ulcer." Wolff and Wolf,[132] in studying a patient with a gastric fistula, found the fasting gastric secretion to be greater during two weeks of intense anxiety than it was in the preceding or following weeks. Hoelzel[57] made a similar observation some years ago, noting that in his own (normal) stomach the fasting secretion in a period of intense marked anxiety lasting two weeks was approximately twice that under normal conditions. Wolf and Wolff[131] also demonstrated in their subject the facility with which an erosion is converted into an ulcer as a result of the continued digestive action of the gastric juice. Mittlemann and Wolff,[79] in 30 unselected patients with peptic ulcer, found variable personality features, but "the reactions of intense anxiety, insecurity, resentment, guilt and frustration obtained in all. . . . it was possible to demonstrate a chronological parallelism between the onset, recrudescence and course of gastroduodenal symptoms, and the occurrence of untoward emotional reactions. . . . The facts of this study emphasize the occurrence in the same individual of the aforementioned destructive emotions coupled with increased motility and secretion and mucosal circulatory changes in the stomach and duodenum, followed by evidence of gastritis and duodenitis, and ultimately actual ulceration. This sequence suggests that the increased circulation, increased motility and disturbed circulation, mucosal erosions and ulcerations are phases of the same process, differing only in the amount of tissue destruction in the stomach and duodenum."

Association With Other Diseases.—Achlorhydria and Atrophic Gastritis.—Peptic ulcer occurs in association with almost all diseases, the notable exceptions being those characterized by complete achlorhydria, namely, pernicious anemia and combined degeneration of the spinal cord. It is rarely, if ever, associated with extensive atrophy of the gastric mucosa, for with that achlorhydria is usually present. With milder grades of atrophic gastritis, however, it is occasionally seen. The relation between atrophic gastritis and achlorhydria is variable. Complete achlorhydria may be present without atrophy, and conversely, normal secretion may be found when patches of atrophic gastritis are observed gastroscopically. With extensive spectacular atrophy of the mucosa, achlorhydria is almost invariably present and ulcer absent. Superficial gastritis and hypertrophic gastritis are frequently seen in patients with ulcer.

Carcinoma.—Gastric carcinoma may appear in association with, but independent of, a healed duodenal ulcer or more rarely with an active ulcer. Carcinoma elsewhere in the body seems to develop as frequently in patients with ulcer as in other persons.

Syphilis.—Syphilitic gastric ulcers are not known to occur with peptic ulcer, but the differentiation may be difficult if not impossible. The positive Wassermann reaction, the achlorhydria, the irregular serpiginous character of the ulcer or ulcers and the tendency of the boggy deformity to simulate carcinoma rather than peptic ulcer may aid in the diagnosis. Benign ulcer not infrequently occurs in the syphilitic; indeed, some physicians consider it to occur more frequently in such persons. Parsons, Plummer, Ewalt and Gaskill[97] found the incidence of peptic ulcer in cases of neurosyphilis to be 10.5 per cent, a higher incidence than that found in cases of latent syphilis and in unselected hospital cases. Occasionally the demonstration of an ulcer deformity or crater in a patient with tabes dorsalis presents a temporary diagnostic problem, but there is usually no difficulty, for the symptoms of peptic ulcer are different from those of tabetic crisis.

Diaphragmatic Hernia.—In diaphragmatic hernias the mucosa at the ring may be the site of erosions or of ulceration, presumably traumatic.

Cirrhosis of the Liver.—Ulcer has been described in association with cirrhosis of the liver,[73] but Schnitker and Hass[114] found only a slightly greater incidence of cirrhotic changes in the liver in patients with ulcer than in normal persons.

Biliary and Renal Calculi.—Cholelithiasis is not infrequently encountered in patients with ulcer, as is renal stone. With the latter association the tendency is to incriminate the alkali therapy—perhaps often correctly, although renal colic is seen in ulcer patients who have not received alkali.[68]

Acute Appendicitis.—Acute appendicitis is a common complication of ulcer, particularly during therapy, apparently resulting from concretions formed by the barium or the insoluble alkali and not indicating any pathologic connection between the stomach, gallbladder and appendix, as is often supposed.

Duodenal Stasis.—Duodenal stasis is commonly described with ulcer. The diagnosis of duodenal stasis, however, as usually made, is rarely tenable, because so-called puddling with some dilatation of the second portion of the duodenum and reverse peristalsis are phenomena seen in normal persons, particularly those with long abdomens.

Polycythemia, Thromboangiitis Obliterans and Heart Disease.—Significance has been attached to the occasional occurrence of ulcer with polycythaemia vera and with thromboangiitis obliterans, but the relation is scarcely sufficient to suggest a correlation.[31] Coronary occlusion occurs with its anticipated frequency. Ulcer may occur and heal in the presence of chronic cardiac decompensation (Fig. 46).

Metabolic Conditions.—Hyperthyroidism and diabetes mellitus each appear from time to time in association with ulcer. Arteriosclerosis occurs apparently with the expected incidence. Active peptic ulcer is rather rarely encountered during pregnancy, although Sandweiss and his associates[107] were able to collect 14 cases of death from perforation or massive hemorrhage during pregnancy or the puerperium.

Essential Hypertension.—Essential hypertension is common with ulcer. Whether this relates to the problem of intracranial lesions, as discussed by Cushing,[33] is an open question.

Pulmonary Tuberculosis and Other Infections.—The frequency of chronic ulcer with pulmonary tuberculosis and other infections, both acute and chronic, seems to be purely a coincidence.

DIAGNOSIS

Symptomatology.—Mechanism of Ulcer Pain.—The outstanding symptom of ulcer is pain.[95] The *mechanism* of *ulcer pain* has long been a subject of study, because of the insensibility of the stomach to ordinary stimuli, such as cutting, tearing, burning and pinching. The epigastric pains or pangs of hunger are due to contractions of the empty stomach, to muscle tension.[22] However, typical ulcer distress is not intermittent as hunger pangs are intermittent, but is steady and continuous, lasting for twenty to ninety minutes or longer. The pain of peptic ulcer is relieved by emptying the stomach and can be reproduced under suitable conditions by reinjection into the stomach of the aspirated material.[85] Typical ulcer distress can also be initiated in subjects with sensitive ulcers by the injection of solutions of hydrochloric acid of physiologic or stronger concentrations. Distress is not produced in normal stomachs by such injections. The evidence that free hydrochloric acid may be an adequate stimulus to the pain-producing mechanism of peptic ulcer may be summarized as follows:[91]

1. With pain attributable to ulcer a high degree of free hydrochloric acid is practically always found.
2. The pain is relieved by emptying of the stomach or by any measure which results in the neutralization of the gastric free acidity.
3. The pain may be relieved by emptying of the stomach and be made to reappear by reinjection of the acid chyme, whereas the injection of gastric contents in which the free acid has been neutralized is not productive of pain.
4. Ulcer pain, typical in kind, location and severity, may be induced under suitable conditions by the injection into the stomach of dilute solutions of hydrochloric acid in perfectly physiologic concentrations (from 0.2 to 0.3 per cent). Dilute solutions of other acids and alkalis (tenth normal solution of sodium hydroxide) also may evoke pain in highly sensitive lesions.
5. Ulcer pain may be induced by the injection of acid gastric juice from another patient or by stimulation of the patient's own gastric secretion with histamine.

Peristalsis and muscle tension[23] are effective in the production of ulcer pain only if the lesion has been sensitized by the presence of acid gastric juice.[85] Continued neutralization results in complete desensitization of the pain mechanism. The evidence suggests that ulcer pain arises at the site of the lesion, that it is not dependent on pylorospasm, gastric motility or intragastric pressure, that the enhanced irritability of the tissue in and about the lesion is dependent on the presence and continued action of acid gastric juice, that the "adequate" stimulus may be either mechanical or chemical and that the *usual* stimulus is the free hydrochloric acid of the gastric content. The daily rhythm of the ulcer cycle is thus related to the variations in the acidity of the gastric chyme. It is important to add that the acidity of the gastric content is not higher in the ulcer patient at the time of pain than in the same patient in a pain-free period at the same point in the digestive cycle or in the average normal person. The difference is that in the patient with ulcer there is a lesion sensitized by the continued action of acid gastric juice, whereas in the normal person no such lesion exists.[87] In certain cases of gastric carcinoma with acid gastric secretion the same mechanism is operative. The pain of ulcer is thus a true visceral pain arising in the ulcer itself. The lesion results from the action of acid gastric juice on inadequately protected tissue. The chemical inflammation lowers the pain threshold of the nerves in the ulcer so that pain may arise from either chemical (acid) or mechanical (peristalsis, spasm, touch, pressure) stimuli. Acid gastric juice is the usual stimulus producing ulcer pain, and it is also the eroding inflammatory agent responsible for the lowering of the pain threshold. Visceral and somatic pain and tenderness differ essentially only in such qualities as the threshold level, the type of adequate stimulus and the degree of localization.[87a] In the so-called silent ulcer, the destructive process apparently takes place without sufficient lowering of the pain threshold to evoke pain.

Characteristics of Ulcer Distress.—The *chronicity* of ulcer distress is illustrated by the fact that in most statistical studies the average stated duration is between five and eight years. Thus, ulcer is relatively benign and chronic. Histories of twenty and thirty years' duration are not uncommon. Occasionally, however, lesions are encountered in which symptoms have been present for only a few days or weeks. A significant percentage (15 to 40 per cent) of acutely perforated ulcers occur in persons who give no previous history of indigestion. In the vast majority of such cases the pathologic evidence suggests a longer duration. The rapidity, however, with which ulcers may come and go has been amply demonstrated in recent years by gastroscopic study.

The *periodicity* of ulcer symptoms is striking. Albrecht[2] found it present in 13 of 21 cases (62 per cent) of gastric ulcer and in 132 of 165 cases (80 per cent) of duodenal ulcer. The usual textbook statement is that the attacks characteristically come in the spring and the fall. Moynihan[80] stated that "the great majority of patients will say that the attacks are especially prone to come in the winter months—December, January or February. In the summer the symptoms are almost always absent." Moynihan ascribed the high winter incidence to " 'getting cold'—the most common of all these causes (of ulcer)." Albrecht found that only 3 of 21 patients with gastric ulcer described a seasonal incidence of symptoms (2 in the spring and fall and 1 in the winter), whereas 55 of 165 patients with duodenal ulcer described such a seasonal recurrence (52 in the spring and fall and 3 in the winter). The distribution of ulcer throughout the year as shown by the month of the x-ray demonstration of the lesion follows:

Month:	1	2	3	4	5	6	7	8	9	10	11	12	Total
Gastric ulcer	4	2	6	4	3	7	5	5	5	4	3	4	52
Duodenal ulcer . . .	38	32	30	17	19	29	14	13	18	27	40	28	305

Perhaps more significant is the percentage of positive results found by Albrecht in the various months of the year:

Month:	1	2	3	4	5	6	7	8	9	10	11	12
No. of duodenal ulcer patients	38	32	30	17	10	29	14	13	18	27	40	28
Total gastric x-ray examinations . . .	147	124	131	118	124	125	149	123	117	126	141	102
Percentage of duodenal ulcers in total gastric examinations . .	25.8	25.8	23.3	14.4	15.3	23.2	9.4	10.5	15.4	21.4	28.4	27.4

It is apparent that for gastric ulcer there is no evidence whatever of a seasonal occurrence. For duodenal ulcer, the lowest absolute and relative incidence occurred in the months of April, May, July, August and September. Yudine,[134] however, in a study of 1,438 cases of acute perforated ulcer, noted a progressive increase in the number of perforations in the winter months, the maximum being reached in the spring. During the summer the number was greatly reduced. The significant point, therefore, is not the spring and fall occurrence but the periodicity.

The periods of distress may be of only a few days' duration, more often of several weeks', and usually of two or three months'. The duration of the periods of remission is even more variable. Usually as the years pass by the periods of distress become more frequent and of longer duration, the distress more severe and the periods of remission shorter. The periodicity of the symptoms is correlated with the pathologic changes, but the cause of the exacerbations is not apparent. Emery and Monroe[37] related the recurrence to acute infections, worry or fatigue, but the evidence for these is scarcely more conclusive than for Moynihan's explanation—"exposure to cold or getting the feet wet, or a hasty or indigestible meal, or worry or overwork. A cause can almost always be assigned for the onset of symptoms(!)"

The distress of ulcer is usually described as a pain. The *quality of the distress* varies. Rarely it may be merely a sensation of fulness or bloating; more frequently it is "heartburn"—epigastric, rather than substernal. The pain is generally described as gnawing; in Germany the adjective most frequently used is cramplike. Other adjectives used at times are aching, hurting, annoying, burning and smarting. Some patients say the distress is a pain for which no adjective is appropriate. Moynihan[80] suggested the term "hunger pain" because it often occurs when the patient is beginning to feel hungry. Some patients, indeed, seem unable to differentiate ulcer distress from real hunger. The pain is usually moderate, occasionally very mild and at times severe enough to suggest perforation or gallbladder colic. It is, as a rule, epigastric, sharply localized to a small area, perhaps 3 to 4 centimeters in diameter, to which the patient is likely to point with the tips of the fingers. Rivers[100] has shown that in duodenal ulcer the distress is likely to be referred somewhat to the right; in gastric ulcer, to the left; in gastrojejunal ulcer, to the left lower quadrant. Back pain may be present with or without epigastric pain, but does not prove, although it may suggest, the presence of a chronic perforation. Ulcer distress may radiate around one or both costal borders. Occasionally duodenal ulcer pain is referred to McBurney's point, which partially explains the number of appendectomies performed for "chronic appendicitis" in patients really suffering from duodenal ulcer. Rarely is ulcer distress referred below the navel. Localization of an ulcer by means of the position of the pain is not entirely accurate. Duodenal ulcer pain, for instance, may be referred occasionally to the left upper quadrant or even through to the back on the left side, just as the pain of biliary colic is at times so referred.

The relation to food taking is more important than is the exact location or the quality of the sensation. A careful and detailed analysis of the "typical day," beginning with the hour of arising, is, therefore, of great importance. Gastric, duodenal and jejunal ulcers cannot be differentiated on the basis of the interval between the meal and the appearance of pain, although distress thirty to sixty minutes after eating is more frequently seen with gastric than with duodenal ulcer, whereas an interval of three or four hours is more characteristic of duodenal ulcer. The pain of peptic ulcer is almost invariably absent in the morning before breakfast, the chief exception being when pain has been present intermittently throughout the preceding night. Rarely there may be slight distress before breakfast in patients without obstruction but with high grade gastric secretion. The distress of ulcer usually appears one to three hours after breakfast. It may last fifteen to twenty minutes and then disappear spontaneously, or it may last until lunch or until food or alkali is taken for relief, when it rarely recurs before lunch. Morning distress may be entirely absent, and is rarely as severe as that in the afternoon or evening. Afternoon distress usually appears one to four hours after the noon meal, lasts from half an hour to two hours and disappears spontaneously or is relieved by the giving of food or alkali, rest or emesis. Evening distress appears at a similar interval after the evening meal and conforms to the same pattern.

Variations in Distress.—*Night Pain.*—Pain usually occurs during the night only if it has been present in the evening and has been relieved with food or alkali. The nocturnal distress characteristically appears between 12 and 2 o'clock. If the patient has eaten before retiring, the pain may appear later. Usually the pain after having once been relieved does not recur during the night or indeed until after breakfast. Practically never does ulcer pain first appear at 3 or 4 o'clock in the morning, provided that dinner the preceding evening has not been followed by distress and that food has not been taken during the evening. Nocturnal pain is generally interpreted as evidence of pyloric obstruction. There are many exceptions. The requisite conditions are a sensitive lesion and a highly acid secretion. Often there is associated pylorospasm or stenosis, either inflammatory or cicatricial, but obstruction need not be present.

Atypical Distress.—Variations in the picture are frequent and at times very confusing. A short acute distress period, of a few weeks or indeed of only a few days, is reported by patients with acute ulcers and by inattentive persons who do not recall their previous attacks of "indigestion." Often a member of the family will give important evidence forgotten by the patient. Daily distress for weeks or months or indeed for two or three years without a significant period of remission is occasionally observed. Complete absence of distress is not infrequent, although the patients do not differ in any known manner from those in whom pain is present. The lesion may be acute or chronic and may manifest its presence by either acute perforation or massive hemorrhage or occasionally be discovered in a routine roentgen or gastroscopic observation. If more routine x-ray examinations of the stomach were made of presumably normal persons, a somewhat higher incidence of asymptomatic ulcer might be found, although judging from observations already made, such lesions would probably not be numerous.

Absence of Food-Relief-Pain Rhythm.—Probably the most frequently encountered variant of the typical distress picture is an absence of relation to food taking associated with failure to obtain relief from food or alkali. This is almost invariably, as Sippy pointed out, a matter either of lack of care in inquiring into the history or of poor observation of the distress by the patient. If one places such a patient in the hospital and carefully observes the relation to food taking, or indeed if one merely asks the patient to keep a detailed hourly diary for a few days, the existence of the typical rhythm is easily shown. However, in occasional exceptional cases the rhythm is actually altered. In very sensitive and acutely inflamed lesions, the pain may be only partially relieved with food. The residue of pain consists usually of soreness, which disappears as a rule in a few hours or, rarely, in a few days, if complete neutralization of the acid is maintained. With such lesions active gastric secretion is usually present, and often there is considerable stenosis. Hour-glass contracture of the stomach occasionally produces a similar alteration of the distress picture.

Biliary and Tabetic Types of Ulcer Distress.—Severe steady continuous pain and vomiting simulating biliary colic and the gastric crisis of tabes dorsalis are rather rare, and their recognition is important, although at times difficult.[52] The vomitus usually consists of either clear or bile-colored gastric juice, highly *acid,* in *marked contrast with the viscid emesis of continued biliary or tabetic vomiting.* The vomiting usually gives only slight and temporary relief, apparently because the stomach rapidly secretes more acid. The diagnosis may be made more difficult still if the patient is known to have cholelithiasis or tabes dorsalis. A further source of confusion is the occasional occurrence of jaundice with duodenal ulcer. The exact mechanism of its production is not clear, although it has been variously ascribed to spasm of the sphincter of Oddi, cholangitis, hepatitis and direct involvement of the common duct in the inflammatory process.

Other Symptoms.—Associated or Incidental.—*Nausea and Vomiting.*—Nausea alone is uncommon with ulcer. Nausea and vomiting may occur together with little or indeed no epigastric pain. Vomiting may occur with little or no nausea and be almost projectile. It is usually due to obstruction at the outlet of the stomach, resulting from pylorospasm, cicatricial stenosis or inflammatory swelling about the ulcer or a combination of these factors. Painless vomiting is usually due to cicatricial stenosis. Incidentally, the absence of pain in many cases of high grade obstruction due to cicatricial stenosis with powerful peristaltic waves visibly distending the stomach and elevating the abdominal wall is evidence that hyperperistalsis and distention of the gastric antrum do not cause the pain of peptic ulcer. Vomiting may occur without obstruction if the pain is severe. In rather rare cases of both gastric and duodenal ulcer without obstruction vomiting occurs without pain. The clinical picture may be that of nervous vomiting and the presence of ulcer not suspected until the roentgen examination is made. The mechanism of emesis in such cases is presumably a simple reflex disturbance of the intrinsic neuromuscular coördination induced by the ulcer.

"Water-brash."—This rather rare symptom seen with ulcer consists of a combination of excessive salivation and acid regurgitation. Patients may be awakened at night by it. Without other symptomatic or objective evidence of ulcer, a positive diagnosis is not warranted.

Constipation and Diarrhea.—Constipation is not an important symptom of ulcer, but is often the outstanding complaint. Many patients either disregard the "indigestion," distress or pain, and hence fail to mention it, or leap to the conclusion that the distress is due to constipation and complain of the assumed cause rather than the pain. Such patients frequently become established cathartic addicts, with resultant bowel dysfunction and abdominal discomfort to confuse the distress picture. Of course, the ulcer may reflexly affect the motility of the bowel, but clinically the other explanations seem more valid. Diarrhea is rarely seen with ulcer except with gastrojejunocolic fistula, of which it is the outstanding symptom. Such a fistula may develop gradually or rather suddenly and *without any pain* either before or at the time of perforation.

Change in Appetite and Weight.—Loss of appetite is unusual, and loss of weight is uncommon, but it may be marked, amounting even to 30 or 40 pounds and thus increasing the clinical suspicion of carcinoma. The weight loss is usually attributable not to loss of appetite but to decreased food intake resulting from fear of eating. With obstruction the weight loss results from continued nausea and vomiting and consequent starvation. Rarely a patient gains weight as a result of increased food consumption in a continued effort to relieve the pain.

Anemia.—The symptoms of anemia usually occur with or subsequent to massive hemorrhage. Not infrequently, however, marked anemia is seen in patients who have not vomited blood or observed the passage of tarry stools. A positive test for occult blood in the stool is obtained in such cases unless the oozing has ceased. Other symptoms of ulcer may be present or absent. The diagnosis of chlorosis may be made erroneously. The patient may become adjusted to the slow loss of blood so gradually that few symptoms arise, as in pernicious anemia, even though the red blood cell count is around 2,000,000 and the hemoglobin concentration 35 to 40 per cent. The diagnosis depends on the history of ulcer-like distress if present, the demonstration of occult blood in the feces, the finding of acid gastric juice and the visualization of an ulcer crater or a deformity with the *x*-ray or gastroscope. The lesion is usually located in the duodenum, but it may be in the stomach, jejunum (anastomotic) or esophagus.

Methods of Examination.—**Physical Examination.**—As Moynihan pointed out, in ulcer "the anamnesis is everything; the physical examination nothing." Often it is possible to elicit rather sharply localized tenderness over the site of the lesion. In the presence of high grade obstruction the outline of the stomach may be visible on the abdominal wall and peristaltic waves observed. Rarely with acutely inflamed anastomotic ulcers a tender mass may be palpable.

Laboratory Examination.—*Gastric Analysis.*—The greatest value of the laboratory examination is in the demonstration of normal conditions. This is particularly true of the gastric analysis, for the finding of acid gastric juice is essential in the diagnosis of active chronic ulcer. The Ewald test meal is simple, and on the whole satisfactory, although a few words should be said regarding the interpretation of the results obtained. It is not permissible to divide persons into groups on the basis of normal acidity, hyperacidity and hypoacidity based on acid values disclosed by the Ewald test meal, for in normal persons all grades of secretion may be found and in a given person variable responses may occur from day to day. The significant fact is the demonstration of free acidity; the exact amount is less important. If no free acid is found with the Ewald test meal, then an alcohol or other fractional test meal, preferably a fractional histamine test meal, should be given.[16] Many physicians prefer the routine use of the latter. It is, on the whole, more satisfactory, although more time consuming. Histamine is the most potent stimulant of gastric secretion known. Histamine curves are usually constant. Histamine achlorhydria, generally speaking, is complete and permanent achlorhydria. There are certain possible errors, however. The tip of the tube may not be in the stomach; it may be in the esophagus or the duodenum. The intern or technician may mix the specimens, or the patient may take an alkaline powder immediately before the aspiration. Schiff has described a thorough study of a case in which there occurred, apparently spontaneously, periods of histamine achlorhydria. In one case (Fig. 50) observed in the University of Chicago clinics, four histamine tests were reported as showing no free acid, but in the fifth examination free acidity was found in ample amounts (*p*H, 1.5).[92] In one of the negative tests the intragastric position of the tip was verified fluoroscopically. Such occurrences are as rare as they are difficult to explain.

In persons with chronic ulcer, acid gastric juice can always be demonstrated, but the amount shown by test meals is variable, as is that of normal persons. There is some evidence[15] that with ulcer there is an excessive continued or fasting secretion not disclosed by the test meal, but conclusive evidence is lacking that such an excessive secretion is always present. The free acid curve (histamine) usually reaches a peak of 100 to 120 clinical units with a ten minute volume of approximately 30 cubic centimeters; the total acidity is of no significance. The maximum *p*H exceeds 3.5 and usually reaches 1.5. The average curve is somewhat higher for duodenal than for gastric ulcer. The pepsin content of the gastric juice is not significantly altered. With marked pyloric obstruction a yeastlike odor may be detected in the gastric content. Microscopic examination then discloses the presence of sarcinae or of yeastlike organisms. Fresh blood is likely to be traumatic in origin, but old blood or "coffee-ground" material usually signifies a bleeding lesion.

Stool Analysis.—The demonstration of occult bleeding is at times of diagnostic value, but it is not essential for the diagnosis of active ulcer; indeed, occult blood is usually absent from the stool.

X-ray Examination.—*Evaluation.*—Of all methods available in the diagnosis of ulcer, *x*-ray examination is the most important. The question may be raised properly whether the *x*-ray picture is more reliable than the history. In the era before *x*-ray, Moynihan, in a consecutive series of 100 operations for duodenal ulcer, erred in the diagnosis in only 3 cases, in all of which gallstones were present, but obviously only the patients with more severe and therefore more definite lesions were submitted to operation.

However, discussion of the relative merits of the history and of roentgen evidence is relatively fruitless, because both are important. In this day and age, failure to use the *x*-ray in the diagnosis of upper abdominal distress or "indigestion" is almost inexcusable. In proper hands and under favorable conditions almost all ulcers, probably 95 per cent, can be demonstrated radiologically. Not only is the clinical diagnosis of ulcer confirmed thus, or indeed made, but valuable information is obtained with regard to the location of the lesion, its size and the complications present. Errors in roentgen diagnosis may be errors of either commission or omission, although usually only the latter receive much consideration. However, the roentgenologist's findings may be indefinite and his conclusion incorrect. Consequently, the clinician in charge must weigh and evaluate all the evidence, clinical and roentgenologic. The *x*-ray evidence may be pathognomonic. Occasionally the clinical evidence is sufficiently conclusive to warrant a positive diagnosis even in the face of negative roentgen and gastroscopic reports, but the diagnosis should be made with some hesitation. The occasion for a purely clinical diagnosis decreases as the proficiency of the roentgenologist increases.

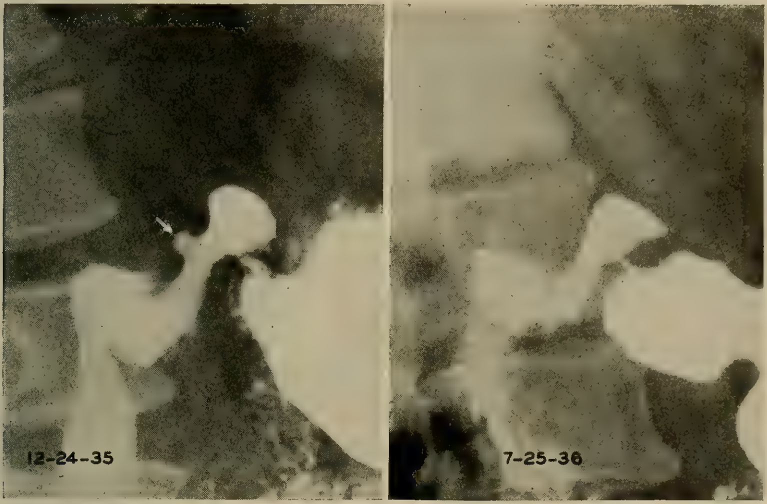

FIG. 48.—Disappearance of the crater (duodenal) and residual deformity of the bulb.

Roentgenologic Criteria.—The direct, or primary, signs consist of demonstration of the ulcer crater or the deformity produced by the ulcer or both (Fig. 48). The indirect, or secondary, signs consist of such nonspecific findings as gastric retention, altered peristalsis and localized tenderness. As a rule it is best to be guided only by the relatively pathognomonic, direct signs of ulcer. The penetrating niche or crater has been accepted as the roentgen evidence of active gastric ulcer (Figs. 48 and 49) since the early work of Barclay[8] and Haudek.[54] For duodenal ulcer, on the other hand, in spite of the early work of Cole,[29] the deformity was the accepted evidence of the lesion until the studies of Akerlund[1] and Berg[12] led to recognition of the frequency with which crater formation can be demonstrated in the bulb, either in the front view or in profile. The crater is the only roentgen sign of active ulcer. It can be demonstrated with proper equipment by skilled and patient roentgenologists in from 50 to 70 per cent of patients with clinical evidence of active ulcer.[120] Crater demonstration is also important in the roentgen diagnosis of anastomotic ulcer. The inexperienced worker will often erroneously diagnose as crater indefinite collections of barium. True craters may occur, of course, at any point along the *Magenstrasse,* in the antrum, in the pyloric ring, in the bulb or

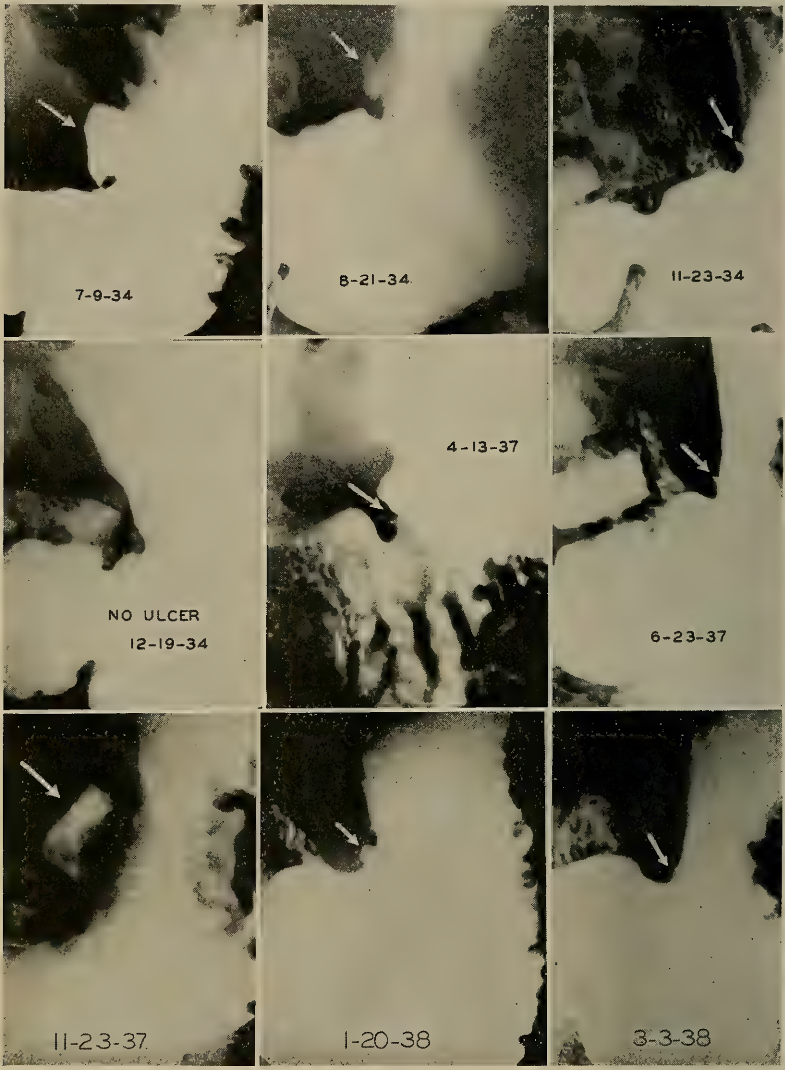

Fig. 49.—The healing and recurrence of a large gastric ulcer in a man aged fifty-three years is evident. Note the gradual decrease in the size of the ulcer from July 1934 to its disappearance in December 1934; the recurrence at the same site in April 1937; the progressive increase in size to November 1937, and the subsequent disappearance of the niche. The patient suffered a recurrence of the ulcer in the summer and fall of 1938, complicated by bleeding and more especially by chronic asthmatic bronchitis, cor pulmonale and cardiac decompensation, from which he died Jan. 24, 1939 (autopsy confirmation). (From Palmer, Schindler and Templeton,[95] courtesy of *American Journal of Digestive Diseases.*)

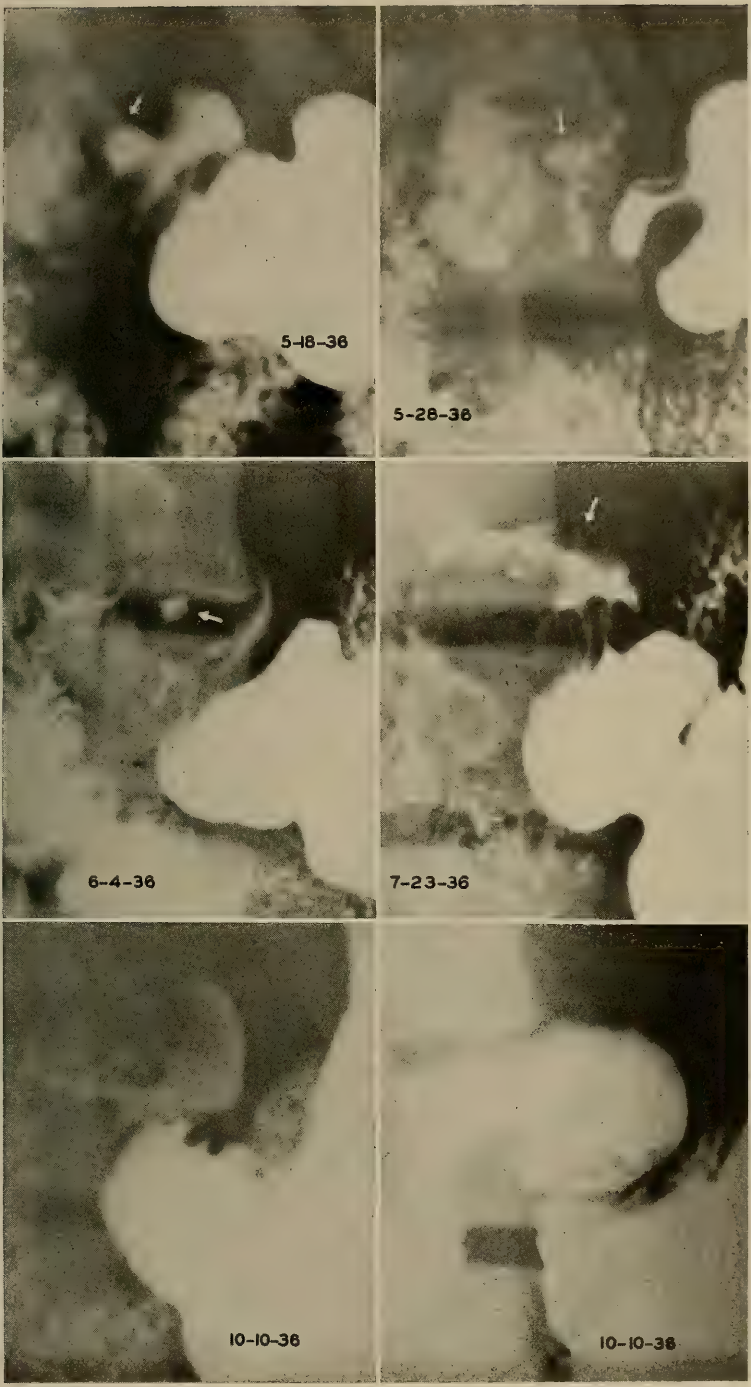

FIG. 50.—The patient, a student aged nineteen years, gave a history of dull, gnawing epigastric pain, coming on three to four hours after meals and relieved by food, for three weeks prior to admission to the hospital. The pain disappeared promptly on the institution of management. The gradual shrinking, fading and disappearance of the crater of the ulcer, with the duodenal bulb returning finally to normal except for a slight distortion of the fold pattern, is clearly seen.

even in the proximal part of the second portion of the duodenum. A genuine crater appears in profile as a penetrating niche or, as it is more typically seen in the duodenum in mucosal relief studies, in the front view as a sharply outlined and circumscribed collection of barium, usually from 2 to 10 millimeters in diameter, surrounded by a halo or a ringlike collar of inflamed and edematous tissue. Occasionally this crater is seen on edge as a linear or oval shadow. In the stomach the rugae typically radiate to it. In the duodenum there are usually shallow or slight folds, also radiating to the crater. The crater typically is to be found at the site of, or just proximal to, the deformity. As the ulcer heals, the crater fades away, decreasing in depth, as a rule, more rapidly than in width. Disappearance of the crater probably precedes complete healing by weeks or months. The deformity produced by an ulcer is usually organic and cicatricial, for it persists after the ulcer has healed. Considerable difference of opinion exists as to whether the gastric hour-glass deformity is spastic or cicatricial. It is difficult to explain its persistence after the ulcer has healed, shown by roentgen and gastroscopic studies, on any other basis than that of scar tissue contraction. Deformities as a rule persist unaltered in the bulb for months and years, and after there is every reason to think that complete healing has occurred. Occasionally, however, one is surprised to find a definite increase in the size of the lumen and a corresponding decrease in the deformity. Deformity of the contour of one or, more frequently, both curvatures of the bulb is present, but craters are seen surprisingly often with no deformity whatever and without leaving, on healing, any scar or deformity discernible by *x*-ray (Fig. 50).

Differential Diagnosis.—Roentgenologically, the differential diagnosis of gastric ulceration consists chiefly in the differentiation of benign and malignant ulcer. The syphilitic and tuberculous ulcers may simulate either of these and are not to be identified on radiologic evidence alone. Definite crater formation in the duodenal bulb is practically pathognomonic of peptic ulcer, but diverticula are often diagnosed erroneously as craters. Under these circumstances symptoms of ulcer are usually present, for diverticula of the bulb are almost without exception pockets formed behind and by scar tissue contraction secondary to ulcer. At the apex of the bulb and in the beginning of the second portion of the duodenum, congenital diverticula occur and may be confused with ulcer craters. Deformity of the bulb is almost invariably attributable to ulcer if it is bilateral and if the incisurae are sharp. Broad unilateral indentations of the bulb usually represent pressure from adjacent organs. A sharp unilateral incisuria of the lesser curvature of the bulb or of the greater curvature near the base usually represents an ulcer scar, but sharp incisurae near the apex constitute less reliable evidence. Not infrequently the first portion of the duodenum has the configuration of a horizontal S, the break in which simulates an ulcer deformity. Rarely indeed does cholecystitis or carcinoma of the gallbladder, biliary ducts, pancreas or duodenum itself produce a deformity resembling duodenal ulcer.

Gastroscopy.—Gastroscopy is of great value in confirming the clinical and roentgen diagnosis of gastric ulcer and at times in demonstrating lesions not seen by *x*-ray. Templeton and Schindler,[120b] in a study of 44 cases of gastric ulcer, found 33 in which the lesion was demonstrated with both *x*-ray and the gastroscope, 4 in which it was seen with the gastroscope and not with x-ray and 7 in which it was seen with x-ray and not with the gastroscope. The two instruments supplement each other. Superficial lesions and the final stages of healing are usually best observed gastroscopically. Anastomotic (jejunal) lesions are often visible through the gastroscope, but usually the x-ray is better suited for their demonstration. Alterations of the gastric mucosa are best studied gastroscopically. In the differentiation of benign and malignant ulcer all the evidence available from the use of both instruments is often needed. The great disadvantage of gastroscopy is the inability to see lesions beyond the pylorus.

Esophagoscopy.—Esophagoscopy is of value in the diagnosis of peptic ulcer of the esophagus. The procedure is more difficult and more dangerous than is examination with the flexible gastroscope and should be performed only by trained and competent workers in the special field. In skilled hands, however, it is very valuable and may be the only way in which a diagnosis of esophageal ulcer can be positively established. The symptoms of esophageal ulcer differ from those of ulcer elsewhere chiefly in that the distress may be more substernal than that with gastric or duodenal ulcer and the passage of food from the esophagus into the stomach may evoke intermittent or persistent pain, variable in degree.

Complications of Peptic Ulcer.—**Perforation.**—*Acute Perforation.*—INCIDENCE.—Not only is acute perforation the most dangerous and the most ominous complication of ulcer, but it is the most common cause of death. In Hurst and Stewart's series[61] acute and subacute perforation accounted for 64.5 per cent of 96 deaths from gastric ulcer and 85 per cent of 200 deaths from duodenal ulcer. It occurs at all ages from infancy to old age and in both sexes, although it is much more frequent in the male. Of the 1,365 patients with acute perforation observed by Yudine,[134] only 26 were women (1.9 per cent)! Winters and Egan,[129] in a study of 360 acute perforations, found about the same high proportion of males, 98 to 2. The ulcer is usually located on the anterior wall of the stomach or duodenum. The ratio of duodenal to gastric ulcer is usually given as 2 or 3 to 1, but Yudine found it to be 9 to 1. The lesion is, as a rule, chronic, although the perforation itself is acute. Multiple perforations at varying intervals are rare. As mentioned previously, a so-called ulcer history may be obtained in 60 to 75 per cent of cases, but it is not essential for the diagnosis. The perforation may be precipitated by straining at stool, coughing, vomiting or other vigorous exertion.

CLINICAL PICTURE.—The symptoms of acute perforation are almost always striking and uniform, and the diagnosis is vividly apparent. Moynihan's[81] description of the symptoms of acute perforation, however, is so superb that the reader is referred to it.

If operation is not performed, generalized peritonitis usually ensues; the abdomen loses its "boardlike character," but not its rigidity or tenderness; it becomes distended; the pulse becomes gradually rapid, weak and feeble; the respirations become more rapid and shallow; hippocratic facies appear, and the patient dies the typical peritonitic death in two to five days.

DIFFERENTIAL DIAGNOSIS.—Differential diagnosis is rarely difficult because the sudden onset of acute agonizing epigastric pain with boardlike rigidity of the abdomen is so typical that other conditions rarely come into consideration. Biliary, renal and intestinal colic lack the boardlike rigidity. Coronary thrombosis likewise lacks the intense abdominal rigidity and is usually accompanied by some radiation of the pain to the precordium, sternum, neck or arms. Lobar pneumonia is almost always accompanied by fever instead of a normal or subnormal temperature. The respiratory rate is increased, and the normal ratio of pulse to respiration, 4 to 1, is decreased to 3 or 2 to 1. There may be some rigidity in the right upper quadrant of the abdomen, but it is much less marked and much less general than that of acute perforation. In the gastric crisis of tabes the abdominal rigidity is absent; Argyll-Robertson pupils are usually present. Acute appendicitis is less severe in its onset; the abdominal rigidity is less intense, and tenderness is maximum near McBurney's point. Occasionally, as Moynihan pointed out, in acute or subacute duodenal perforations the fluid flows down around the outside of the ascending colon and collects in the right iliac fossa, resulting in maximum tenderness there, which simulates acute appendicitis. In mesenteric occlusion and intestinal obstruction, the pain is rhythmic and intermittent; the abdominal rigidity is less marked. The rigidity is much less marked also in ruptured ectopic pregnancy, and the pain and tenderness are in the lower part of the abdomen. Perforation of the gallbladder is usually indistinguishable from that of the stomach or duodenum, except that the former typically occurs during or after the apparent subsidence of an acute cholecystitis. However, the pain of acute cholecystitis and of duodenal ulcer are often confused.

Most difficult is the differentiation of acute perforation of ulcer from acute pancreatitis. The known presence of gallstones and of obesity are helpful, for Griessmann[51] found a relation between pancreatic necrosis and biliary tract disease in 94.2 per cent of his series of 80 cases of acute pancreatitis. Ninety per cent of the patients in his series were female and 10 per cent male, but other writers have not reported such a high preponderance in the female. The pain of acute pancreatitis may be even more acute than that of acute perforation, and marked shock is almost always present. Usually, the abdominal rigidity is not so intense or widespread, and the tenderness is less complete than it is in acute perforation. Jaundice, usually very slight, is present in about half the cases, and a peculiar but characteristic slate-blue tinge often develops at an early stage. This is most distinct in the lips, in the lobes of the ears, in the face, and in the fingernails. Berg[11] has observed roentgenologically extreme distention of the stomach and transverse colon by air (meteorism) in acute pancreatitis, in contrast to the x-ray demonstration of free gas in the peritoneal cavity in acute perforation. Elman[36] found marked elevation of the blood amylase the most important diagnostic clue to acute pancreatitis.

Acute perforation is rare with ulcer on an adequate therapeutic program, whereas acute appendicitis is rather frequent. Also, peptic ulcer of the esophagus, although rare, has a tendency to perforate in an acute, subacute or chronic fashion into the mediastinum, pleura or pericardium.

Subacute Perforation.—Subacute perforation presents similar but less intense symptoms. There is the same sudden onset of intense pain, usually with vomiting with more or less prostration. The rigidity is usually localized in the upper part of the abdomen. The perforation is quickly plugged by adhesion to other structures, and there is little or no escape of fluid from the stomach or duodenum. The pain gradually subsides in eight to ten hours, and the condition of the patient improves markedly. Complete healing of the ulcer usually ensues, although occasionally a localized abscess may form or the fibrinous barrier may break and generalized peritonitis result.

Chronic Perforation.—Chronic perforation scarcely warrants detailed consideration. The base of an ulcer not infrequently is formed by the capsule of the pancreas, of the liver or indeed of some other adjacent structure, such as the anterior abdominal wall, the transverse mesocolon or the colon itself. The tissue of the adjacent organ is less frequently invaded. Chronic perforation does not particularly modify either the symptoms or the course of the lesion. Rather surprisingly, a jejunal ulcer may perforate into the colon without any pain, the first and only symptom being diarrhea.

Acute Perforation and Massive Hemorrhage.—Acute perforation may occur in the presence of hemorrhage. Winters and Egan[129] found that 36 of 360 acute perforations occurred in patients whose ulcers had bled. In 14 of the 36, massive hemorrhage had occurred one to seven days before, and in 9, eight to fifteen days before; in 13 there had been intermittent bleeding for fifteen days to one year. They thus proved the fallacy of the oft-repeated statement that bleeding ulcers do not perforate and perforating ulcers do not bleed. Another fallacy is the statement that ulcers do not recur after hemorrhage or perforation, for recurrences are frequent after both complications.

Massive Hemorrhage.—*Incidence.*—Massive hemorrhage, much more frequent and much less severe than acute perforation, has an incidence estimated by Hurst and by Crohn at about 10 per cent. From 20 to 25 per cent of all patients with ulcer experience massive bleeding at some period. Ulcer is the most frequent cause of bleeding from the upper part of the digestive tract. Any ulcer may bleed, but the ulcer located on the posterior wall of the duodenum seems particularly prone to do so. Fatal hemorrhage is practically always arterial in origin. At autopsy a branch of the pancreaticoduodenal, coronary or splenic artery, or perhaps even the main vessel itself, is found protruding from the base of the ulcer, usually surrounded by scar tissue and as a rule more or less sclerosed. The mortality rate has varied from 1.5 to 20 per cent or even higher in certain small series. Kirsner and Palmer,[65] in reporting 230 cases, described 5 deaths from exsanguination and 3 from complications—a total mortality rate of 3.47 per cent. For 65 patients aged fifty or more years, the mortality rate was 7.6 per cent, as compared with 1.8 per cent for the 165 patients under fifty. The concept that the mortality rate rises with each recurring hemorrhage was not substantiated.

Symptoms.—Ulcer-like symptoms had been present for one to ten years in 110 (47 per cent) of the 230 cases, ten to twenty years in 58 (25.2 per cent), twenty to thirty years in 21 (9.1 per cent) and over thirty years in 15 (6.5 per cent). In 22 (9.56 per cent) no history of ulcer was elicited or the symptoms had been present for less than one year. While massive hemorrhage from ulcer may occur in the complete absence of pain or other symptoms immediately preceding it, hemorrhage is always evidence of extension or penetration of the ulcer process, just as perforation is. It is rarely seen in patients under treatment in the hospital or in patients continuing an adequate therapeutic regimen outside.

The symptoms of acute hemorrhage are classic. With gastric ulcer hematemesis is usually present; with duodenal ulcer it is present in about one-fourth of the cases. Melena is almost always present. Winters and

Egan[129] have shown that only 60 cubic centimeters of blood is required to produce a tarry stool. The concomitant symptoms depend largely on the severity of the hemorrhage and consist of faintness, weakness, dizziness, headache, perspiration, thirst, dyspnea, syncope and collapse. In instances of moderate bleeding there may be only hematemesis or the passage of one or more tarry stools or both. With more pronounced bleeding there may be sudden weakness, dizziness and fainting, perhaps accompanied by hematemesis followed by the passage of loose, tarry stools. The fainting is apparently due to the rapid drop in blood pressure and resultant cerebral anemia. Usually the vasomotor system regains its tone rapidly; the blood pressure rises, and the patient may feel and appear only slightly disturbed by the episode. With severe hemorrhage, however, the blood pressure usually remains below 100 and often below 90; the pulse rate more or less gradually increases, and the patient continues in shock. The more marked and persistent the drop in the blood pressure and the more rapid and weak the pulse, the greater is the danger. In the first hours the blood count may be normal except perhaps for the moderate leukocytosis of hemorrhage. The drop in the red cell and the hemoglobin level appears later, as the total blood volume is restored. A moderate azotemia occurs, resulting from the digestion and absorption of blood.[110] Patients almost never die immediately, although in one patient found dead in bed autopsy disclosed a huge dilated stomach filled with clotted blood. Death usually occurs two to five days after the onset, or even later in certain cases, and results directly from exsanguination or from some complication like lobar pneumonia. Recovery is the rule, however. After the bleeding has stopped, its source should be ascertained if possible. If no lesion is found, the diagnosis of an acute ulcer or an erosion may be hesitatingly made.

Other Causes of Hematemesis and Melena.—Peptic ulcer is the common cause of hematemesis and melena at all ages. The role of the so-called hemorrhagic diathesis in gastrointestinal hemorrhage, with or without ulcer, is largely speculative. Gastrointestinal bleeding may occur, however, with any of the so-called blood dyscrasias—leukemia, hemolytic icterus, purpura, hemophilia, splenic anemia and Hodgkin's disease. In one case of Hodgkin's disease fatal bleeding occurred from an ulcer located in the bulb and apparently secondary to the Hodgkin's disease, for a granulomatous lymph gland formed the base of the ulcer. Acute gastrointestinal bleeding may occur rarely in the course of any acute febrile illness. As a rule, however, massive hemorrhage may be considered as coming from one of three sources: peptic ulcer, acute or chronic, including erosions; carcinoma, and esophageal varices. *X*-ray and gastroscopic examinations are not usually carried out until several days or even weeks after the cessation of the bleeding. Complete healing may have occurred, and hence no lesion may be demonstrated. Under such circumstances particularly, the other two possibilities must be borne in mind. Massive hemorrhage in the course of, or as the initial symptom of, gastric carcinoma is not as rare as is generally supposed. The bleeding may cease completely; the stools may show no occult blood; the radiologic examination may give negative results, and yet a carcinoma may be demonstrated later, perhaps with a recurrent hemorrhage. Histamine anacidity with massive hemorrhage always raises the suspicion of carcinoma. Esophageal varices are also rather common and can usually be demonstrated roentgenologically.

The spleen is almost invariably enlarged and palpable. Cirrhosis of the liver may be present, but there are now many instances on record of splenomegaly and esophageal varix with a normal liver. In fact, in my experience the liver has usually been normal.

Malaena Neonatorum.—The frequency of peptic ulcer in the newborn is not generally appreciated. Hurst and Stewart[60] stated that in 50 per cent of the infants dying from melena the bleeding is due to peptic ulcer, and pointed also to the work of Theile,[121] who found records of 64 cases of melena among 204 cases of acute ulcer in infants newborn and under a year old. The onset of melena occurred most frequently on the first day of life and was never delayed beyond the fifth, the majority of patients dying within four days and none later than a fortnight after birth. Hematemesis occurred often and perforation in 20 per cent.

Obstruction.— *Definition.*—The term is rather loosely used in describing persistent vomiting, the vomiting of food eaten the previous day or failure of the stomach to empty properly, evidenced by abnormal gastric retention of a food or barium meal or by the presence of unusually large quantities of food in the routine evening aspirations. "Obstruction" and "retention" are not synonymous and should not be so used. Retention may be present without gastric disease on a purely nervous basis, as with headache.

Evidence of Obstruction.—The *vomiting* of food eaten the previous day usually denotes obstruction, but emesis *per se* is not evidence of obstruction.

Dilatation of the stomach with hyperperistalsis is present, as a rule, with marked obstruction. This is particularly true if it is possible, as the patient lies supine, to see the outline of the distended stomach through the anterior abdominal wall and to see peristaltic waves of sufficient power to lift up the abdominal wall. For such obstruction it is customary to distend the stomach with carbon dioxide. The patient is instructed to drink half a glassful of water containing a teaspoonful of sodium bicarbonate, followed by a half glassful of water containing a teaspoonful of tartaric acid. The latter should be drunk slowly and the abdomen examined after every few swallows. The normal stomach can be outlined, but normal peristaltic waves can be seen only if the abdominal wall is very thin and relaxed. With a good abdominal musculature the demonstration of peristaltic waves running from left to right across the stomach is almost pathognomonic of obstruction; the presence of reverse peristalsis is definitely so. The demonstration in the gastric aspiration of food eaten the day before also usually means obstruction, for simple retention is rarely of this grade.

The finding in the gastric content of *food eaten the previous day or of sarcinae or yeast* indicates retention so continued as to be pathognomonic of obstruction. The presence of the yeastlike organisms may often be suspected from the yeasty odor of the gastric content.

The amount of *gastric retention* may be estimated after a "motor meal": 100 Gm. each of cooked potato, spinach, carrots and raw apple, one egg, one slice of bread with a square of butter, 15 Gm. (dry weight) of tea leaves and beverages as desired. This should be eaten when the stomach is empty, and no further food or drink should be taken until after the stomach has been aspirated with the Ewald tube seven hours after the end of the meal. The aspiration should yield only 1 or 2 ounces of liquid with a few leaves of tea or spinach. Larger amounts are rarely encountered in the normal stomach unless headache, nausea or some other disturbing factor is present. The stomach should then be washed by injecting and aspirating several bulbsful of water. The washings should return clear. A four, five or six hour barium meal may likewise be given and the amount of retention noted roentgenologically. Retention may or may not be indicative of obstruction.

Obstruction may be due to stenosis at the site of the ulcer or to failure of the pylorus to open. The *exact location* of the ulcer is of considerable importance in determining the mechanism of the obstruction and consequently in evaluating the significance of the obstruction and the therapeutic procedures to be employed. Careful roentgen examination aids so greatly in locating the site of the lesion, the site of obstruction and the degree of obstruction that it is more valuable, on the whole, than all other procedures combined.

Ulcer of the lesser curvature of the stomach not infrequently occurs with or in the presence of hypertrophic stenosis of the pylorus. It is difficult to decide which is primary. The combination has several times been observed in men over fifty years of age who gave no history of vomiting or of epigastric distress before the age of fifty. In one such patient the surgeon confirmed the diagnosis of hypertrophic pylorus. In at least one other patient with this condition the pyloric obstruction persisted after the ulcer had healed, as shown by both roentgenologic and gastroscopic studies. The pyloric narrowing may be due to a healed prepyloric ulcer, as in a case observed recently in which the ulcer seen roentgenologically on the lesser curvature 4 or 5 centimeters proximal to the pylorus was found at operation to be associated not with hypertrophic stenosis, but with a second, healed ulcer just proximal to the pyloric sphincter (Fig. 48). Narrowing of the pyloric antrum[95] may or may not be present and may persist after healing of the ulcer. Golden[46] has related this antral narrowing to an "inflammatory reaction of the gastric wall." Templeton and Schindler,[120]. however, were not able to confirm this gastroscopically. Ulcers in the pyloric ring or impinging on the pyloric ring from either side are usually accompanied by rather persistent closure of the pylorus, presumably pylorospasm. This seems more likely if the ulcer is on the gastric side. Such lesions usually heal slowly, if at all, and are prone to recur. They seem to heal with considerably greater difficulty than ulcers 1 or 2 centimeters proximal to the pylorus.

With duodenal ulcer the obstruction may be due to the failure of the pylorus to relax; if so, it usually disappears under treatment. It is important to ascertain the width of the channel at the site of the deformity, which may be due to spasm, inflammatory swelling or cicatricial contracture. If there is much spasm, it is usually evident from the irritable, irregular action of the pylorus and the bulb, and subsides after a few days of treatment. The actual narrowing appears to be chiefly cicatricial, for it usually does not change much in weeks or months of treatment. Occasionally, however, it changes a great deal, and one is surprised to find a lumen 5 to 10 millimeters in diameter instead of 2 to 4 millimeters. The lumen of the normal bulb is usually 2 or 3 centimeters in diameter. If it is decreased to 5 or 10 millimeters, the stenosis is moderate; to 2 to 4 millimeters, marked, and to a hairline or 1 millimeter, high grade and usually accompanied by gastric dilatation, ballooning of the antrum and hyperperistalsis. The maximum width of the channel should be determined fluoroscopically

—not from the film, which often is exposed at the moment the muscle is in contraction, thus suggesting high grade stenosis when it is not present. While obstruction is generally considered the most frequent complication of ulcer, surgical treatment is as a rule not indicated unless the stenosis is marked.

Hour-glass Contracture.—The hour-glass deformity is generally secondary to gastric ulceration, usually benign, and occasionally to neoplasm or to syphilis. Rarely does it result from external adhesions and then not in marked degree. With diaphragmatic herniation of the stomach an hour-glass deformity is usually present. Strangely, hour-glass contracture is usually seen in females rather than males, the ratio being 8 or 9 to 1. In approximately half of the cases autopsy shows the ulcer healed. The lesion may be located at any point along the lesser curvature and the contracture at a corresponding point on the greater curvature. The incisura is sharp and often seems to extend to the lesser curvature, but rather rarely does it produce high grade stenosis. The result is usually a bilocular, or maybe a trilocular, stomach. The history is, as a rule, of many years' duration; the distress is mild; vomiting may be present; massive hemorrhage or perforation may occur. Not infrequently the patient describes hemorrhage or perforation rather early in life, followed by many years of chronic "indigestion." There may be an associated pyloric lesion. Operation is not generally required. The true hour-glass contracture is almost always cicatricial, not spastic, but may be accentuated by spasm. It may involve chiefly the mucosa, and hence its extent may not be apparent from the external appearance of the stomach. Furthermore, it is much less marked in the contracted empty stomach than in the distended full stomach. A picture simulating hour-glass contracture may be produced by the indentation of the greater curvature by the ribs or colon.

The Gastric Ulcer–Carcinoma Problem.—Differentiation of Benign and Malignant Gastric Ulcer.—*Clinical Criteria.*—The ordinary ulcerating gastric carcinoma is so typically malignant that benign ulcer does not come into consideration. Difficulty arises with those lesions which simulate benign ulcer. The differential criteria are, on the whole, relative rather than absolute. The age of the patient is of some importance, but gastric carcinoma may occur in the third decade of life, and benign ulcer is common in the sixth and the seventh. The duration of the distress is also important, in that a long history suggests a benign lesion whereas a short history is more in accord with a diagnosis of neoplasm. However, chronic symptoms may be entirely unrelated to the gastric lesion under consideration, and conversely, a benign ulcer is often rather acute, with symptoms of only a few months' duration. If distress has been present for several years and then changes qualitatively as well as quantitatively, one suspects malignancy. Such changes, however, occur with a benign lesion also. Periodicity is an important, although not invariable, feature of benign ulcer, but it may occur to a certain degree with malignant ones[42] As a rule, however, periodicity is absent completely with carcinoma or at least is much less definite than is usual with peptic ulcer. The relation of the distress to eating, with relief after the taking of food or alkali or after vomiting, typical of ulcer, is frequently seen in carcinoma and hence is of little differential value. Loss of appetite is much more characteristic of carcinoma, but it may occur with both conditions, as may loss of weight and loss of strength. Hematemesis, coffee-ground vomitus and melena occur with both diseases and may be the initial symptom of either. The continued presence of occult blood in the stool after two or three weeks of careful treatment is presumptive evidence of malignant change, whereas the continued absence of occult blood suggests that the lesion is benign. A sufficient number of exceptions occur, however, to show that the presence or absence of occult blood in the feces is not pathognomonic of either a malignant or a benign lesion.* Gastric analysis should never be omitted, for the diagnosis of chronic benign ulcer should not be made in the presence of continued and complete histamine anacidity. Histamine achlorhydria in the presence of a questionable penetrating gastric lesion speaks almost unequivocally for carcinoma, as do large numbers of lactic acid (Oppler-Boas) bacilli and lactic acid. High acid values, on the other hand, such as 100 to 110 units after histamine administration, are frequently encountered with carcinoma. All these clinical data must be carefully correlated with the roentgen and gastroscopic evidence.

Roentgen Criteria.—The *x*-ray interpretation of a given ulcer is generally more or less accurate, not absolute, and depends on certain factors such as the location of the lesion, its size and depth, its relation to adjacent structures and the character of the surrounding mucosal pattern. Ulcers of the greater curvature are almost always malignant. Rivers and Dry[101] found records of only 4 benign ulcers of the greater curvature in the files of the Mayo Clinic. Matthews[76] in 1935 found only 22 cases reported in sufficient detail in the literature to warrant such a diagnosis. The antrum is the favorite site for the development of carcinoma, being involved in 82 per cent in the experience of Konjetzny.[67] Graham[48] found 94 per cent of ulcers between the incisura and the pyloric vein histologically malignant. Holmes and Hampton[58] likewise stated that the majority of prepyloric ulcers are carcinomatous. Lehmann,[69] on the other hand, found benign prepyloric ulcer frequent. In my experience benign prepyloric lesions are not infrequent.[95] The size of the lesion is of relatively little value in the differentiation, for small lesions may be carcinomatous,[89] and many large craters are benign (Fig. 49). The crater of the benign ulcer usually appears, roentgenologically, to extend beyond the normal confines of the gastric lumen, whereas carcinomatous craters do not. This relation, depending largely on the location and depth of the crater and whether it is seen in front view or in profile, is of limited value. The swelling about the ulcer crater, appearing usually as a halo brought out by manual pressure, may be seen with both lesions. With benign ulcer it is due to inflammatory swelling and edema, and with malignant ulcer to neoplastic infiltration with more or less inflammation. The parallel rugae tend to be abruptly interrupted by the carcinomatous ulcer, whereas in benign ulcer they usually converge to the lesion. The meniscus sign of Carman,[24] consisting of an ulcer crater located beneath the level of the lesser curvature and demarcated by a zone of tumefaction appearing as a halo, almost invariably denoted carcinoma. The greater the distance of the lesion from the lesser curvature, the greater the likelihood of carcinoma, but many lesser curvature lesions are malignant. The crater of a benign ulcer is, as a rule, smooth or slightly irregular, and that of a malignant ulcer is often so; but markedly irregular or ragged craters are almost always malignant. The irregularity is due to the ragged edge of carcinoma or to the nodules of tumor tissue, which also account for the coarse, nodular or at times polypoid appearance occasionally seen in the zone about the malignant ulcer. Finally, under adequate therapy the benign ulcer rapidly diminishes in size, while a carcinomatous ulcer may decrease by a fourth or a third, but rarely more. Complete disappearance of the crater roentgenologically, with the restoration of a normal mucosal relief pattern, speaks almost overwhelmingly for a benign lesion (Figs. 49 and 51). The importance of the normal mucosal pattern is illustrated by figure 52. In this case the crater of the ulcer disappeared, but the infiltration of the gastric wall persisted. The ulcer had partially healed by the proliferation of both neoplastic and apparently normal mucosa. The malignant nature of the lesion was evident from the mucosal relief pictures and also from the gastroscopic studies.

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* The student and practitioner should keep this differentiation uppermost in mind in evaluating the evidence because, in my personal experience, it has been exceedingly helpful.—EDITOR.

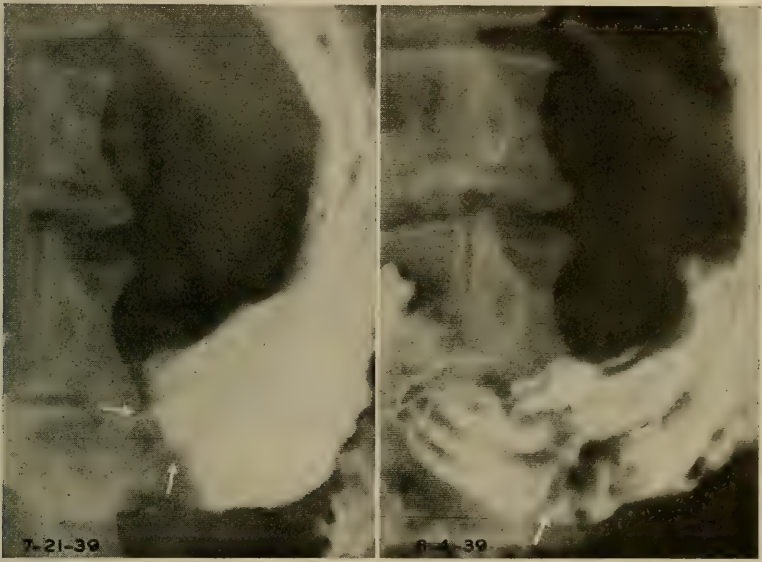

FIG. 51.—The patient, a woman aged thirty-nine years, entered the hospital July 22 with severe, cramplike epigastric pain occurring two or three hours after meals periodically for a year, increasing in severity, waking her at night and relieved by milk so effectively and so frequently as to have led to a 30 pound gain in weight in ten months. The rapid decrease in the size of the crater on the posterior wall of the stomach during two weeks of treatment is well shown. Fluoroscopic examination confirmed the evidence of the film. There was no occult blood in the stool. The maximum free acid (histamine) was 100 clinical units.

Gastroscopic Criteria.—The gastroscope, like the x-ray, is of great value, but like the x-ray, it is not infallible. Prepyloric ulcers or ulcers of the upper posterior wall of the lesser curvature may be difficult to visualize; they may be seen poorly, or they may not be seen at all. If the ulcer is seen clearly, the appearance may be characteristic of either a benign ulcer or a carcinoma, or it may be equivocal. Often the most valuable information is obtained by carefully observing the course of the lesion from week to week during intensive treatment. The benign ulcer, according to Schindler,[111] is generally crater-like—rarely shallow; its floor is whitish yellow—not often brownish, although after an acute hemorrhage it may be dark red; its edges are sharp and often partly undermined. The adjacent mucosa of early lesions is often normal; later there may be marked inflammation of the surrounding mucosa but rarely of the entire stomach. Converging folds occur. The carcinomatous ulcer, however, is characterized by less sharp edges, so that the ulcer floor seems to blend with the mucosa. The floor is irregular and contains nodules, nodes or ridges. It is occasionally whitish or yellowish but more frequently brown, brown-red, violet, gray or a dirty color. The malignant ulcer is usually elevated, appears to lie on a hill and therein differs from the benign ulcer. The adjacent mucosa may be nodular. Schindler contended that it is easier to differentiate benign and malignant ulcer gastroscopically than by gross examination of the resected specimen because of the color nuances produced by the circulating blood and also perhaps because of the stiffening produced by the submucosal infiltration. Gastroscopic differentiation, in Dr. Schindler's hands at least, is usually correct, but exceptions do occur. This is, of course, to be expected if one bears in mind that in certain cases the extent and the characteristics of carcinomatous gastric ulcer are largely determined by the same destructive factor that operates in benign ulcer, namely, acid gastric juice.[94] Therefore, the two lesions may mimic each other completely, and, indeed, cases have been reported in which the ulcers were histologically benign, presumably because of complete digestion of the tumor, and yet carcinoma was found in the adjacent lymph glands.[43]

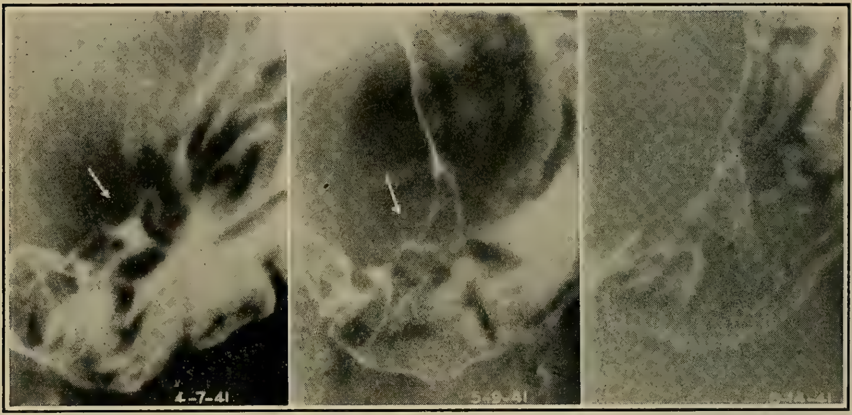

Fig. 52.—Ulcer in a woman aged forty-one years. The ragged crater present April 7 was not seen on May 9 or June 14. Note the absence of the normal mucosal relief pattern at the site of the ulcer, with evidence of infiltration of the wall, in all three films. The patient had experienced cramping epigastric pain without remission for two years. For six months prior to admission the pain had been gnawing, related to and relieved by food taking. The maximum gastric free acidity (histamine) was 50. With hospitalization and a milk and cream diet the pain subsided in a few days. The crater disappeared, but the neoplastic nature of the lesion, evident roentgenologically and gastroscopically, was proved by resection June 20. At the center of the infiltrated area were two ulcers each measuring about 1.0 × 0.6 cm. but only 1 mm. deep. The microscopic diagnosis was carcinoma simplex.

Conclusions.—It is apparent, therefore, that one or more of the various differential points outlined may give conclusive proof that the lesion is malignant, but not, on the other hand, that it is benign. *Conclusive clinical proof of the benign nature of an ulcer consists in the roentgen and gastroscopic* *demonstration of complete healing, with return of the gastric wall to normal* (Fig. 51). In practice it is safe to consider a sharply circumscribed, penetrating lesion of the lesser curvature as tentatively benign, providing the stomach is found able to secrete acid gastric juice. Such a lesion may be treated medically, provided the diagnosis is clearly recognized as provisional only. Relief from pain and gain in weight are to be expected and are not very reassuring, but failure to obtain relief may be significant. The occult blood should disappear from the stool completely in two or three weeks if the lesion is benign and continue if it is malignant, but exceptions occur. The crater should be studied roentgenologically and gastroscopically at weekly or biweekly intervals and should decrease in size rather rapidly. Usually the benign ulcer improves so rapidly from week to week that one feels amply justified in continuing the observation, whereas the malignant lesion changes little, if at all. When the ulcer is completely healed and the gastric wall is normal, as shown by direct roentgen and gastroscopic evidence, malignancy is excluded with reasonable certainty.

Carcinomatous Transformation of Benign Ulcer.—*Statement of the Problem.*—For many years carcinomatous transformation has been considered a complication of gastric ulcer, but not duodenal, jejunal (anastomotic) or the relatively rare esophageal ulcer. Konjetzny[67] related gastric ulcer and gastric carcinoma to gastritis and expressed the belief that carcinoma may arise from the proliferating changes occurring in the healing phases of gastritis or ulcer. Bloomfield[14] endorsed this concept and concluded that the crucial factor in the diagnosis of "cancer *ex ulcere*" is the presence of acid gastric juice. Carcinomas with achlorhydria, he stated, are carcinomas of gastritic origin. The problem under discussion, however, is that of carcinomatous transformation of peptic ulcer, or carcinoma *ex ulcere.* Does it occur? The answer must be based on clinical and pathologic data, for there is no experimental evidence. Proof of such a transition must consist of conclusive evidence, first, that a benign gastric ulcer was originally present and, second, that the ulcer underwent carcinomatous change.

Clinical Evidence.—The clinical evidence of preëxistent ulcer usually consists of a long history of the ulcer type. This is most inconclusive, for the distress may not have been due to ulcer at all, or it may have been due to ulcer and yet the ulcer have been entirely independent of the carcinoma, as in the case reported by Singer[117] and in the 33 cases of associated duodenal ulcer and gastric carcinoma reported by Wilbur and Rivers.[126] The stomach is, after all, the internal organ most frequently afflicted with carcinoma. Indeed, Livingston and Pack[70] stated that "approximately one-third of all malignant tumors are located within the stomach" and that "there are more deaths from cancer of the stomach than from all malignant tumors of lip, tongue, cheek, tonsil, pharynx, larynx, salivary glands, thyroid, male and female breast, ovary, uterine cervix and corpus uteri *combined.*" A long history of the ulcer type is therefore not significant evidence that the gastric carcinoma is *related* to a preëxisting ulcer, if present. Furthermore, gastric carcinoma may be more chronic than is generally appreciated. Eusterman and Balfour[42] described a case of carcinoma with achlorhydria in which symptoms had been present preiodically for seven years. The findings, including a palpable mass, were typically those of a polypoid carcinoma of the middle third of the stomach. The patient refused operation, improved at a health resort and gained 16 pounds. The symptoms apparently recurred about two years later. An "ulcerated polypoid adenomatous carcinoma, grade 2" was removed two and a half years after the diagnosis had been established, nine and a half years after the onset of symptoms. Nine years later, at the age of seventy-five, the patient was still in excellent health.[39] Other evidence exists of the extreme chronicity of certain carcinomas, such as the recorded instances of recurrent tumor twelve and fifteen years after subtotal gastric resection.[88] In one case studied by Palmer, Schindler and Templeton,[95] a small gastric ulcer appeared carcinomatous both gastroscopically and roentgenologically for four years, and yet at the time of operation was still small, easily resectable and without evident metastases.

Certain evidence[7] tends to show that gastric ulcers do not have a tendency to carcinomatous transformation. As Hurst and Stewart[61] remarked, "The figures show that malignant disease develops no more often in a stomach in which there is a scar of a healed ulcer, or even occasionally a still unhealed ulcer, than in one from which an ulcer has been excised!" Bloomfield's[14] conclusion that the presence of acid gastric juice is the "crucial factor in the diagnosis of cancer *ex ulcere*" cannot be accepted, for the clinical evidence of preëxistent ulcer in his cases was inadequate. Furthermore, gastric free acidity has disappeared during carcinoma,[102] Apparently no one has followed the course of a typical peptic ulcer roentgenologically and gastroscopically for several years with healing and remission and then witnessed its transformation into a carcinoma. Such observations would be highly significant.

Pathologic Evidence.—The pathologic evidence may be divided into, first, that of preëxistent benign ulcer and, second, that of carcinoma. According to Newcomb,[83] the signs of preëxistent benign ulcer consist of:

(*a*) Complete destruction of an area of muscle corresponding in size roughly to the floor of the ulcer; (*b*) the presence of a large area of dense fibrous and granulation tissue in the floor of the lesion; (*c*) the presence of endarteritis obliterans or thrombophlebitis in the vessels around; (*d*) fusion or close approximation of the muscularis mucosae and muscularis at the margin of the ulcer. All these points are usually, but not invariably, present in chronic peptic ulcers.

The only sign of benign ulcer never found in primary carcinoma, according to Newcomb, is the "fusion of the muscularis mucosae and muscularis at the edge of the ulcer. It is suggested that the presence of this criterion is as valuable as the demonstration of tubercle bacilli in the diagnosis of tuberculosis!" Gomori,[47] however, found fusion in only 34 of 64 cases of chronic peptic ulcer. Fusion was noted in 4 of the 6 cases accepted by Gomori as instances of carcinomatous transformation of benign ulcer. The duration of symptoms in 1 of these cases was one year; in 2 it was three years. The evidence for preëxistent benign ulcer in these 3 cases must therefore be seriously questioned, and the validity of Newcomb's pathognomic sign likewise. It is apparent that the various pathologic criteria of previous benign ulcer are not conclusive.

In the pathologic diagnosis of carcinoma the classic criteria are usually present. The diagnosis, however, may be debatable if it is based on the cytologic appearance of certain cells in the edge of an ulcer, "atypical hyperplastic cells" morphologically indistinguishable from gastric cancer cells, for the alteration seen in different types of cells in response to injury is generally indistinguishable morphologically from that of malignant cells.[59] The presence in opposite edges of an ulcer of morphologically different types of carcinoma is sometimes cited as proof of malignant transformation, but is not conclusive. Saphir[109] has found morphologic variations among the individual tumor cells of particular neoplasms. Ewing[43]. has also noted that multiple sections from the same carcinoma may disclose great variations in structure, explicable in part by the "occurrence of multiple areas of early cancer in a localized area" and the fact that "if an adenocarcinoma extends laterally by ulceration then it may encounter in its advance a second or third focus of primary carcinoma."[44] This multicentric origin of gastric carcinoma is supported by a great deal of evidence. The ulceration may extend beyond the tumor on one edge; it may leave only a small nodule of tumor on one edge, or it may completely destroy the primary growth.[43]. . Apparently, then, the clinical and pathologic evidence adduced to support the concept of carcinomatous transformation of benign ulcer is inconclusive and the two common lesions of the same organ may be considered independent of each other until proved otherwise. The ease with which they can be differentiated and the therapeutic implications, however, are another study.

TREATMENT

General Considerations.—Indications for Treatment.—Of course, the first step in therapy is the establishment of the diagnosis. However, the evidence may be merely suggestive or unequivocal, and judgment is therefore required as to whether to go ahead with treatment or await the development of further evidence. The history may be so definite as to constitute more or less positive proof, but despite this, the complete examination should be carried out, including in all cases an *x*-ray study of the esophagus, stomach and duodenum and in many cases a gastroscopic examination. It is important to determine definitely the location and size of the lesion with the complications present. If the ulcer is not actually found, the differential diagnosis must include a consideration of other causes for the symptoms present. Failure to demonstrate the ulcer does not invalidate the diagnosis, but it does make it much less conclusive. When the ulcer is demonstrated, the diagnostic problem then concerns the type of ulcer, *i. e.*, peptic, neoplastic, syphilitic or tuberculous. Other conditions, such as cholelithiasis, do not invalidate the diagnosis of ulcer, although they raise a question as to the origin of the symptoms. When there is definite, or under certain circumstances presumptive, evidence of active ulcer, therapy may be instituted.

The Two Problems of Therapy.—Two fundamental and distinct, although related, problems are present regardless of whether ulcer is considered a thing unto itself or an incident in the course of a chronic general or local disease, such as chronic gastritis, the "antral gastritis" of Konjetzny or *Ulkuskrankheit ohne Ulkus.* These problems are the healing of the ulcer and the prevention of its recurrence. The former is usually easier than the latter. As a matter of fact, spontaneous healing frequently occurs, as is evident not only from the periodicity of the symptoms but from the common demonstration of healed scars at autopsy and at *x*-ray examination. Gastroscopy has also shown the remarkable tendency of the lesions to heal and recur. Certain persons known as "ulcer formers" or "intractable cases" are said to possess the vague "ulcer diathesis" and exhibit a strange and persistent tendency to formation of new ulcers almost as rapidly as the old ones can be healed or removed surgically.[55]

Healing.—The first task of therapy, however, is to bring about not merely a disappearance of the crater, but a complete *restitutio ad integrum* with a normal glandular mucosa (Figs. 46 and 47). It is almost impossible for the clinician to know when this has occurred, for the symptoms may vanish weeks or months before the crater disappears roentgenologically and gastroscopically, and an additional period must necessarily elapse before the thin layer of epithelial cells is transformed from squamous to columnar cells and then into normal mucosa. Hence, symptomatic relief and disappearance of the occult blood from the stool do not constitute adequate evidence of the course of the lesion. Roentgenologic and, for gastric ulcer, gastroscopic studies should be made at intervals, for if a crater can still be demonstrated, healing certainly cannot be said to have occurred. However, the roentgenologist occasionally is able to hold a small collection of barium, usually poor outlined, in the depression of a healed ulcer and may have difficulty in differentiating this shadow from the crater of an active ulcer. The gastroscopist also may at times find it somewhat difficult to determine the exact phase of healing. Nevertheless, roentgen and gastroscopic study provide the most definite evidence obtainable and should be utilized whenever possible (Fig. 53).

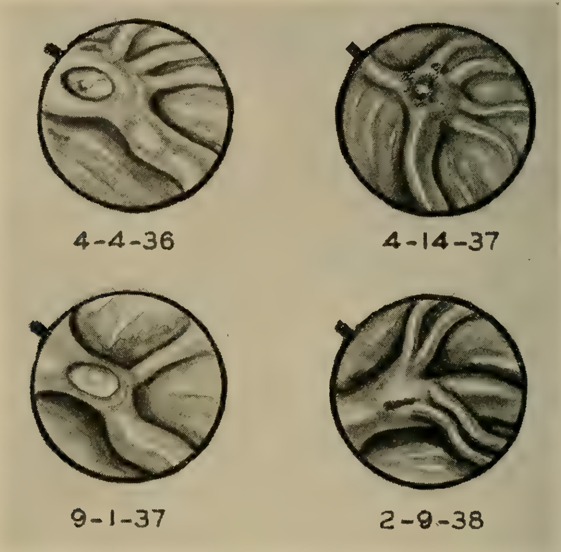

FIG. 53.—Gastroscopic evidence of healing and of recurrence in a woman, aged sixty-three. Note the definite decrease in the size of the ulcer from April 4, 1936, to April 14, 1937, the ease of localization by means of the characteristic pattern of the folds, the increase in the size of the ulcer from April 14 to Sept. 1, 1937, and the subsequent healing by Feb. 9, 1938. The mucosa is essentially norma. (From Palmer, Schindler and Templeton,[95] courtesy of *American Journal of Digestive Diseases.*)

Recurrence.—Recurrent ulcer is more or less frequent after any and all forms of treatment, whether medical or surgical, except total gastrectomy! The recurrent lesion may be the old ulcer undergoing an acute exacerbation, a new lesion at the same site or an entirely new ulcer. Recurrence of course raises the etiologic question again. Emery and Monroe,[37] in an extensive study, found the three most frequent causes to be fatigue, worry and infection. These are, of course, the most frequent and common forms of stress in life, and hence it is not surprising that the recurrences should be attributed to them. Conclusive proof of their significance is lacking, but they should not be ignored in the treatment of ulcer or indeed of any chronic disease. Regardless of their role in the recurrence of ulcer, however, prophylaxis is closely related to treatment of the lesion itself. The old adage" once an ulcer patient, always an ulcer patient" has in it sufficient truth to justify prolonged therapy and, whenever needed, an intelligent reorganization of the patient's life.

Medical Treatment of Benign Ulcer.—The "Therapeutic Fallacy."—For any chronic disease like peptic ulcer the course of which is characterized by remissions and exacerbations, the evaluation of therapy is difficult. The "cures" for ulcer are legion, and most of them will be discarded as their predecessors have been. The annual crop of popular new "cures" is due to many factors: (1) prevailing methods of treatment are not completely satisfactory; (2) the periodicity of the disease leads to false evaluation of the efficacy of the therapy under consideration;[106] (3) the factor of mental suggestion enhanced by the enthusiasm of the physician is extremely important yet difficult to assay,[6] and (4) the physician and the patient both succumb to the lure of new fads properly advertised.

Management of Peptic Ulcer.—*Rationale.*—Sippy was the first to develop a comprehensive program of therapy[19] based on the premise that "the greatest known hindrance to the healing of peptic ulcer that is amenable to medical or surgical control . . . is the disintegrating and digestive action of the gastric juice." Once this is removed, "Nature . . . fills in the defect with granulation tissue and cicatrization of the ulcer may occur approximately as rapidly as it does elsewhere on other surfaces of the body." This concept not only has stood the test of time but has been strengthened by the additional clinical and experimental evidence obtained. There would be no ulcer problem if it were possible and practical to bring about complete and permanent gastric anacidity. The program devised by Sippy aims at "maintaining an accurate neutralization of all free hydrochloric acid during the time that food and its accompanying secretion are present in the stomach."[86] This condition is difficult to maintain. The continued secretion of acid gastric juice during the night is even more difficult to control than the day secretion, as Sippy appreciated. The measures available for this purpose are in general those inhibiting gastric secretion and those neutralizing the acid secreted.

Rest.—For most diseases rest is important; for some it is essential; for ulcer it is very valuable. The rest should be both physical and mental, but what is rest? The poet John Sullivan Dwight sang, "Rest is not quitting the busy career, Rest is the fitting of self to one's sphere." Rest does not necessarily consist of hospitalization or of confinement in bed. A rather strenuous hunting or fishing trip may prove more restful for a tired person than a period of worry in a hospital. Often, however, not even a vacation provides mental rest, for it may not be possible to run away from the basic emotional conflicts or problems. However, the worry and turmoil of life may be minimized by helping the patient to gain clearer perspectives and different attitudes. There may be much expressed or suppressed anxiety about the disease itself, about the fear of cancer, about the economic burden entailed and about the possible inability to work. Explanation and reassurance are invaluable in gaining the patient's coöperation and confidence and often in helping him to regain confidence in himself. Faith is essential, for it brings release from fears and apprehensions. Faith in the future, faith in a "cure," faith in a physician or faith in almost anything may restore emotional tranquillity to a worried and harassed patient. The role of anxiety is illustrated by the story of a man with a difficult recurrent jejunal ulcer whose poor renal function precluded the use of alkali. His livelihood depended on his ability to judge the "market." Its daily fluctuations kept him in constant turmoil. Finally, a wealthy friend presented him with a three months' de luxe trip to Europe. On the third day out from New York the distress disappeared and, despite repeated dietary and alcoholic insults to the ulcer, did not recur until a few weeks after his return to the routine stresses of life and his constant anxiety over the stock market. The therapeutic use of "de luxe trips" has many limitations. There are, however, various ways of promoting emotional calm. Usually it is best accomplished indirectly by assurance, encouragement and sympathetic understanding while detailed attention is directed to the treatment of the lesion itself. Confidence in the physician comes when the patient knows not only that he feels well but that scrupulous care is being exercised in the management of the lesion.

Physical rest, preferably more or less complete rest in bed for two or three weeks, is generally more desirable in the treatment of ulcer than a fishing trip. The period can be one of mental and emotional as well as physical rest during which the physician educates the patient in adherence to a meticulous program of therapy. Hospitalization is highly desirable, for the education is more easily accomplished and the patient is relieved of the cares of home. He learns that other people have ulcers; that his condition is not unique; that others carry out the program; that it is "the thing to do." Patients who have been hospitalized usually give better coöperation in the carrying out of a long program of therapy than those who have been treated at home or while ambulatory. Home management may be perfectly satisfactory if there are no domestic tensions and if the program is adequately supervised. The desirable duration of bed rest is variable. Usually it is best to compromise between that which is desirable and that which is necessary. Two weeks should be the minimum; two months is about the maximum period needed. A longer period of relative rest may be advantageous, but is not imperative. For difficult lesions and for patients able to afford it, six months or a year of freedom from work and worry is very salutary. More important, however, is the understanding on the part of the patient that certain restrictions or regulations of his program of life are definitely in order; that he is confronted with the problem not merely of healing the ulcer in question but of preventing its recurrence.

Diet.—The diet should be soft and nutritious. It is not necessary to pay particular attention to the quantitative differences in gastric secretion which presumably result from the ingestion of different foods, for these variations are relatively slight. All foods and liquids, including water, stimulate gastric secretion. Fats do exert a moderate inhibitory effect on gastric emptying and on secretion. The acid-combining capacity of protein food is significant. Consequently, a mixture of milk and cream or high protein milk is superior to skimmed milk or whole milk[64] (Fig. 54). Sippy used a mixture of milk and cream in order to obtain these neutralizing and inhibiting effects and because of its nutritive value. The usual schedule consists of the administration of 90 cubic centimeters of equal parts of whole milk and 18 per cent cream hourly from 7 A.M. to 7 P.M. It may be modified, if desired, in various ways, such as by using whole milk alone, skimmed milk or powdered milk, or by varying the quantity. Occasionally vanilla or chocolate may be added as flavoring, but rarely does the patient choose to continue the use of these. If distaste for the milk and cream arises, alkalosis may be suspected. Sometimes an aversion for cream develops and whole milk is more pleasing. A small amount of orange juice, perhaps 1 ounce hourly, is often helpful at this stage. Rarely indeed is a patient actually unable to tolerate milk. Many persons think they are unable to digest milk or that they are sensitive to it, but when hospitalized and induced to take milk, they are able to do so. If they actually are sensitive to milk, some form of desensitization apparently occurs, for the ability to tolerate it develops. If a loss of weight is desired, whole milk or skimmed milk may be used. More frequently a gain in weight is in order, not only because the patient is under-weight but because wound healing may progress more satisfactorily if the patient is in the good nutritive condition evidenced by increasing weight. The hourly allowance of milk and cream may be increased from 90 to 120 cubic centimeters and malt may be added, but such a mixture is usually too sweet to be taken for

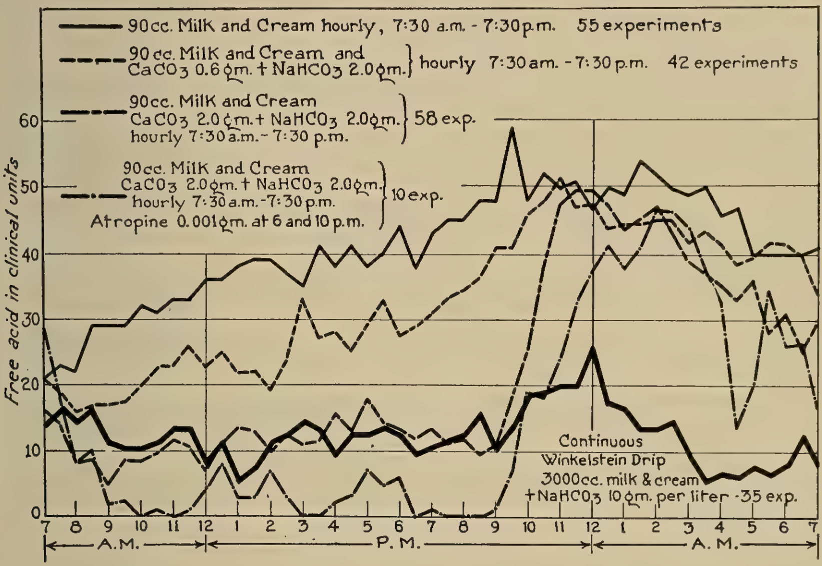

FIG. 54.—The reaction of the gastric content with various regimens. Note: 1. The best neutralization of the daytime free acidity was obtained with milk and cream and alkali given during the day and atropine given at 6 and 10 P.M.The 2. best control of the night secretion was obtained with the Winkelstein drip. 3. The night secretion was somewhat *greater* when *no* alkali was given during the day than it was when alkali was administered. (From Kirsner and Palmer,[64] courtesy of *American Journal of Digestive Viseases*.)

more than a few days. There is no need to worry about the vitamin intake during the few days for which the diet is restricted as outlined, but orange juice and various vitamin preparations may be given if desired. The caloric and vitamin values for the basis programs used are shown in Table 1.

Table 1.—Caloric and Vitamin Contents of Ulcer Management Diet With Various Modifications*

						Vitamins					
							B₁ Thiamin		C (mg.)	B₂ (mg.)	
	Hrs.	Carbohydrate	Protein	Fat	Cals.	A (I.U.)	Mg.	T/NFC†	Ascorbic acid	Riboflavin	D (I.U.)
Milk, 45 cc.; cream, 45 cc.	7–7	58	36	128	1,528	2,965	0.45	1.3	14	1.08	303
Skim milk, 90 cc.	7–7	59	35	12	484	23	0.58	1.6	0	1.20	0
Whole milk, 90 cc.	7–7	59	35	47	799	2,012	0.50	1.4	15	1.20	20
Evaporated milk and water, 90 cc.	7–7	59	35	47	799	2,480	0.29	0.84	15	2.30	20
Milk and cream, 90 cc.; malt, 100 Gm.	7–7	126	52	137	1,945	3,205	0.70	1.0	14	1.27	303
Milk and cream, 90 cc.; chocolate sauce, ½ cup	7–7	194	58	145	2,313	2,965	0.45	0.49	14	1.08	303
Milk and cream, 90 cc.; 1 additional feeding	7–7	81	40	138	1,726	2,965	0.45	1.3–	14	1.08	303
Milk and cream, 90 cc.; 2 additional feedings	7–7	91	46	145	1,853						
Milk and cream, 90 cc.; 3 additional feedings	7–7	116	53	164	2,148						
Milk and cream, 90 cc.; 4 additional feedings	7–7	134	58	166	2,262						
Milk and cream, 90 cc.; 5 additional feedings	7–7	179	70	185	2,661						
Milk and cream, 90 cc.; 6 additional feedings	7–7	186	71	191	2,747						
3 meal ulcer management		180	85	185	2,735	11,977	0.77	0.8	73	1.65	580
Requirements (normal standards)						3,000 to 6,000	0.6 to 2.0	0.8 to 1.0	15 to 75	2 to 3	700

* I am much indebted to Miss Margaret Ahern, dietitian, for valued help in the preparation of this and the following tables.
† Thiamin-nonfat caloric ratio.

Additional feedings with or instead of the milk and cream may be instituted at once or deferred for several days. Usually it is satisfactory to begin with one small additional feeding on the second or third day and add one every other day until six are being given. This schedule has a definite psychologic value in that it gives the patient something to anticipate from day to day and enables him to see progress. If the stomach empties quickly and an immediate gain in weight is desired, the additions may be made earlier and more rapidly; if, on the other hand, moderate obstruction is present, they may be delayed. The foods allowed and the manner in which they are added to the diet is shown in Table 2. A rigid form is not necessary, but the schedule shown in Table 3 has been found highly satisfactory. The weight curve is almost as important as the temperature chart. During the first few days of management a loss of weight is expected, but by the end of the first week the weight should begin to increase, reaching the admission weight by the end of the second week. Continued weight loss usually means not only inadequate food intake but high grade obstruction, although the latter can be judged better by the quantity of gastric content aspirated at bedtime and the other criteria described.

TABLE 2.—ADDITIONAL FEEDINGS FOR ULCER MANAGEMENT

For feedings 1, 2 and 3 select from the following list:

Cream of wheat
Farina
Boiled rice
Rice baked in milk

Soft cooked egg
Poached egg

Bavarian cream
Spanish cream
Lemon sponge
Grape sponge
Blanc mange
Cornstarch pudding
Tapioca custard
Vanilla custard
Caramel custard
Icecream
Whipped cream
Chocolate sauce
Plain jello

When four feedings are ordered, the following foods may be added to the foregoing list:

Toast
Toasted crackers
Milk toast
Bread pudding

Soft scrambled eggs
Soft omelet

Angel cake
Sponge cake
Arrowroot wafers
Vanilla wafers
Plain cake

- Strained cream soup
  - Rice
  - Celery
  - Carrot
  - Asparagus
  - Pea
  - Potato
  - Spinach
  - Tomato

When five and six feedings are ordered, use food from the foregoing lists.

TABLE 3.—SCHEDULE FOR ADDITIONAL FEEDINGS

Days	8 A.M.	10 A.M.	NOON	2 P.M.	4 P.M.	6 P.M.
1	...	...	Farina and cream			
2	...	...	Boiled rice and cream			
3	Farina with cream and sugar	...	Custard and cream			
4	Rice with cream and sugar	...	Jello with whipped cream			
5	Farina with cream and sugar	...	Vanilla icecream	...	Blanc mange	
6	Rice with cream and sugar	...	Tapioca cream	...	Floating island	
7	Poached egg on toast	Custard	Icecream with chocolate sauce	...	Strained cream of pea soup, crackers	
8	Farina with cream and sugar	Milk toast	Strained cream of asparagus soup, toast	...	Jello with cream	
9	Soft cooked egg	Custard	Icecream	Strained cream of potato soup	Rice custard	
10	Farina with cream and sugar	Poached egg on toast	Milk toast	Sponge cake with whipped cream	Strained cream of celery soup, toast	
11	Rice with cream and sugar	Soft cooked egg, toast	Icecream, vanilla wafers	Bavarian cream	Bread pudding	Strained cream of carrot soup
12	Poached egg on toast	Farina with cream	Milk toast	Floating island	Jello with whipped cream	Strained cream of rice soup, toast

Ordinarily the patient is ready some time in the third week to begin the so-called three meal management program, consisting of a generous breakfast, dinner at noon, a light supper and the hourly milk and cream feedings between meals. The details of this schedule, given to the patient at the time of his discharge from the hospital, are as follows:

Ulcer Management Instructions

The treatment begun during the hospital stay is to be continued with the modifications to be described. An ulcer heals slowly, and several months are usually required. The patient is expected to report regularly to the out-patient department, where the progress will be observed and supervised. Changes in the management may be made from time to time.

All foods must be puréed, cooked soft or well chewed, in order that they may be reduced to a state of fine subdivision before they are swallowed. All highly seasoned foods are to be avoided.

The powders and milk and cream are to be taken at the regular intervals specified, in order that the acid in the stomach may be neutralized throughout the entire day. The milk and cream mixture should consist of equal parts of whole milk and 20 per cent cream. A 1 quart thermos bottle will carry a day's supply. The aspirations at night serve to empty the stomach and to show whether the acid has been properly neutralized.

The patient should aspirate the stomach every night thirty minutes after taking the last powder, emptying the stomach entirely; measure the contents removed; record the amount obtained and the reaction, and bring the record to the out-patient clinic. A streak of blood in the gastric contents is of no importance.

If continued headaches, nausea or extreme malaise appear at any time, the powders should be discontinued, and the patient should report at once to the out-patient clinic. If the stools become *black* and *tarry*, or if a *sudden severe pain* develops anywhere in the abdomen, the patient should report to the hospital or out-patient clinic *at once*.

DIET

Breakfast

- 1 serving of:
  - Fruits
    - Orange juice
    - Peach purée
    - Applesauce
      - Baked apple (no skin)
      - Prune purée
      - Pear purée
      - Apricot purée
    - Cereals
      - Cream of wheat
      - Oatmeal (well cooked)
      - Boiled rice

- Eggs (1 or 2)
  - Soft cooked
  - Soft boiled
  - Soft poached
  - Scrambled with milk and butter
  - 1 or 2 slices of toast and butter
  - 1 cup coffee
    - Tea
    - Sanka
    - Chocolate
  - Cream and sugar as desired

Dinner

- Soups (strained cream soup)
  - Rice
  - Pea
  - Potato
  - Celery
  - Spinach
  - Lettuce
  - Asparagus
  - String beans

- Scraped beef
- Minced beef or diced beef with gravy
- Small portions of roast
  - Lamb
  - Beef
  - Mutton
- Broiled steak and lamb chops may be taken after two or three months if thoroughly masticated
- Bread and butter as desired

1 serving of
  Carrots
  Tomato
  Baked potatoes
  Mashed potatoes
  Rice
  Spaghetti
  Macaroni
  Noodles
Vegetables, strained or puréed or cooked until soft
  Carrots
  Beets
  Asparagus
  Green beans
  Peas
  Squash
  Spinach
Meat: 1 small serving of
  Roast chicken
  Stewed chicken
  Broiled whitefish

Desserts
  1 serving of
    Bavarian cream
    Lemon sponge
    Grape sponge
    Blanc mange
    Cornstarch pudding
    Tapioca custard
    Vanilla custard
    Icecream
    Sponge cake
    Angel cake
    Ladyfingers
    Arrowroot cookies
    Vanilla wafers
    Plain cake
    Jello with whipped cream
    Caramel custard
    Cream cheese

Supper

Cream soup (see noon list)

Rice *or*
Cream of wheat *or*
Soft egg

Crackers *or*
Buttered toast

Desserts (see noon list)

Milk and Cream and Powder Schedule

8:00 Breakfast
8:30 Powder
9:00 Milk and cream
9:30 Powder
10:00 Milk and cream
10:30 Powder
11:00 Milk and cream
11:30 Powder
12:00 Dinner
1:00 Powder
1:30 Powder
2:00 Milk and cream
2:30 Powder
3:00 Milk and cream
3:30 Powder
4:00 Milk and cream
4:30 Powder
5:00 Milk and cream
5:30 Powder
6:00 Supper
7:00 Powder
8:00 Powder
9:00 Powder
9:30 Aspirate stomach; record amount and reaction

The average caloric and vitamin contents of this program are adequate. The patient is instructed to report to the out-patient clinic or office at approximately monthly intervals for *x*-ray or gastroscopic examinations or for such changes and instructions about his regimen as may be indicated. The management should generally be followed rigidly for a year or eighteen months and then modified.

Antacids.—Alkali of various types, but particularly calcium carbonate, has been used from time immemorial in the treatment of peptic ulcer. The salts of sodium, bismuth, calcium, magnesium and aluminum have enjoyed popularity at different times. Sippy used bismuth subcarbonate, sodium bicarbonate, calcium carbonate and heavy magnesium oxide. The standard powders for many years were (1) 2 Gm. of sodium bicarbonate combined with 0.65, 1.3 or 2 Gm. of calcium corbonate and (2) 0.65 Gm. each of magnesium oxide and sodium bicarbonate. These powders have excellent neutralizing value. The number of magnesium powders needed daily depends on the condition of the bowels: some patients do not require any; others require three or four or more. If too many are given, diarrhea and abdominal distress ensue; if too few, fecal impactions in the rectum or the sigmoid flexure may result.

The alkali should be given hourly from 7:30 A.M. to 7:30 P.M. and at 8, 8:30 and 9 P.M. It is not sufficient to give one or two doses after each meal. Wosika and Emery,[133] however, found that the milk and cream and powder could be given together at hourly intervals with as satisfactory neutralization as when given separately. The choice of the alkali to be used varies with the individual. The soluble sodium bicarbonate is likely to produce alkalosis, but the insoluble salts of calcium, magnesium and aluminum do not do so. However, the loss of gastric chloride by aspiration or vomiting may produce severe alkalosis without the administration of any alkali. Calcium carbonate is probably the most effective neutralizer of acid.[77] Magnesium oxide is a splendid neutralizer of acid, but it is highly laxative. The other salts of magnesium, such as magnesium carbonate, are less laxative and on the whole effective. The colloidal preparations of aluminum should be used in relatively larger doses. Theoretically the neutralizing capacities of the various antacids, expressed in the number of cubic centimeters of 0.5 per cent hydrochloric acid (0.143 normal) neutralized by 1 Gm. of alkali, should be as follows:

1. Magnesium trisilicate, 192 cc.
2. Calcium carbonate, 140 cc.
3. Tribasic calcium phosphate, 90 cc.
4. Sodium bicarbonate, 83 cc.
5. Aluminum hydroxide, colloidal suspension, 40 cc.

The values actually found *in vivo*[65] do not correspond with the theoretical, nor indeed with those obtained *in vitro* by Freezer, Gibson and Matthews.[45] Many factors are involved, such as solubility, rate of reaction, limits of reaction, the rate of gastric emptying and the rate of gastric secretion. The more rapid the emptying, the greater is the difficulty in neutralization, and *vice versa*. While evidence on the effect of alkalis on both gastric emptying and gastric secretion is conflicting, clinical experience shows that even if they increase gastric secretion, they may nevertheless be given in sufficient amounts to accomplish neutralization. Kirsner and Palmer[64] found that the night secretion was not greater when alkalis were given during the day than on the same schedule without alkalis (Fig. 54).

Opinions and tastes differ as to the choice of alkali and the dose. If an attempt is made to maintain complete neutralization of the free acidity, *i. e.*, a pH of 3.5 or less, it is necessary to follow an hourly or semihourly program such as that of Sippy. The neutralizing value of this milk and cream program, consisting of administration of 90 cubic centimeters of half milk and half cream hourly from 7 A.M. to 7 P.M., should be supplemented by powders given hourly with the milk or cream or preferably from 7:30 A.M. to 7:30 P.M. and at 8, 8:30 and 9 P.M. Calcium carbonate in 2 to 4 Gm. doses is satisfactory, *provided strict attention is paid to the bowels and sufficient magnesium carbonate powders (2 Gm. each) are substituted for the calcium carbonate to prevent fecal impactions in the rectum.*

Fecal Impactions.—When straight calcium carbonate alone is used in large doses, special attention must be given to preventing rectal or sigmoidal impactions. This is best accomplished by alternating the calcium and magnesium powders until a mild diarrhea ensues and then determining just how many magnesium powders the patient requires to maintain either normal bowel function or perhaps a slight diarrhea. Rectal impactions must be broken up digitally at once and removed manually or with large enemas. The procedure should be continued until rectal examinations prove the rectum to be empty. At times the rectum is found filled with soft putty-like material which the patient is also unable to expel. Large soapsuds enemas and rectal examinations must be continued until the rectum is empty. In rare instances a large calcium stool may lodge in the lower part of the descending colon or in the sigmoid flexure. The clinical picture of paralytic ileus may ensue. Under such circumstances, the best procedure is watchful waiting, including the application of heat to the abdomen in the form of hot stupes or an electric pad, the use of a Wangensteen tube for relief of the nausea, vomiting and distention and frequent rectal examinations to determine whether the stool has yet moved down into the rectum. Warm oil retention enemas, 3 to 6 ounces, may be helpful, but repeated large water or soapsuds enemas are likely to produce further distention of the abdomen without bringing the fecal mass down into the rectum.

Aspiration of the Stomach.—The routine bedtime emptying of the stomach is important for several reasons: (1) It provides a check on the degree of neutralization obtained. If carried out approximately half an hour after the administration of the last powder, the aspirate should contain no free acid, unless the dose of alkali is inadequate or unless the stomach empties rapidly, discharging the powder into the duodenum, in a few minutes, after which the stomach secretes the 20 to 40 cubic centimeters of clear gastric juice subsequently aspirated. When larger quantities are obtained, neutralization is usually observed if adequate amounts of alkali have been given. Failure to obtain neutralization may provide an indication for increasing the amount of the powder. Further evidence of the degree of neutralization may be obtained by sampling the gastric content at other times of the day, perhaps routinely at 4 P.M. three times per week. (2) It empties or nearly empties the stomach and thus, by inducing a fasting phase, decreases the period during which the ulcer is bathed with acid gastric content. (3) It reminds the patient that the evening meal should be small, that powders should be taken during the evening and that his regimen is definite. To the uninitiated the suggestion of psychologic value from the gastric aspiration may seem absurd, but this value is real.

Patients almost without exception quickly adjust themselves to the ordeal of aspiration, learn the technic and become able to carry out the procedure by themselves for days, weeks or months and, indeed, in rare instances for years. At the time of discharge from the hospital the patient purchases an aspiration outfit, consisting of an Ewald bulb and tube, a measuring glass and Töpfer's reagent. The great majority of patients are discharged from the hospital with instructions to carry on the regimen until further instructions are given. When the quantity of gastric content obtained regularly does not exceed 30 to 75 cubic centimeters, the nightly aspirations may be discontinued.

Night Secretion.—After the stomach is emptied, it usually continues to secrete rather large quantities of highly acid gastric juice, as Sippy an his colleagues recognized and as Winkelstein[128] and other workers have since shown. This secretion may continue all night and is apparently rather characteristic of the stomach with ulcer. A routine midnight aspiration three or four times a week after the 9:30 bedtime aspiration may disclose 30 to 100 cubic centimeters of highly acid gastric content.

Similar evidence may be obtained by periodic aspirations through a Rehfuss tube allowed to remain *in situ* all night. This excessive continued night secretion is not induced by the administration of alkali (Fig. 54); it continues a real problem, and for this reason the hours of 6 and 10 P.M. have been chosen for the administration of atropine. Often it is well to give 4 Gm. of calcium carbonate with a small amount of water at 10 P.M., and occasionally at midnight, 2, 4 and 6 A.M. Even this program may not accomplish complete "control." It may be well in rare cases to give milk and cream through the night as well as powders, or to use a continuous drip.

Antispasmodics.—The accepted role of atropine in the treatment of ulcer is that of an antispasmodic, although clinically it is difficult to prove that atropine lessens so-called pylorospasm or spasm at the site of the ulcer. There is conclusive evidence, however, that atropine in adequate doses does diminish gastric peristalsis and secretion.[99] Kirsner and Palmer[64] found that neutralization of the acid is more readily obtained with alkali when atropine is given, probably owing to both decreased secretion and decreased emptying. The maximum dose tolerated, 1 mg. at 6 P.M. and 1 mg. at bedtime, may produce unpleasant dryness of the mouth and throat with a loss of the usual power of accommodation. Other antispasmodics have been advocated, but there is little, if any, evidence that they are more selective in their action on the stomach than atropine or superior to it.

Other Methods of Therapy.—*Drip Treatments.*—The administration of food or antacid or both by means of a continuous drip into the stomach has much to recommend it. The feeding is in effect a fistula feeding, eliminating the potent cephalic phase of gastric secretion. Neutralizing material can presumably be given at a sufficient rate to offset the gastric secretion. More complete control of the acidity of the gastric content can be maintained by the day and night use of the drip method than by any other procedure. It is useful in certain cases for the initial stages of healing, or indeed it may be possible to continue it until complete healing has occurred, although usually this is not the case. Rarely is healing complete in less than three or four weeks. The drip method is not usually continued for more than a week or ten days, occasionally two or three weeks. The patient must continue to follow a carefully regulated program thereafter in order to bring about complete healing and prevent recurrence. Disadvantages are the complete rest in bed required (which may be an advantage!) and dryness of the throat leading perhaps to the development of pneumonic complications, esophagitis or esophageal ulceration. Winkelstein[128] advocated the administration through a nasal catheter of milk containing 5 Gm. of sodium bicarbonate per liter, at the rate of 1 liter per eight hours. A colloidal suspension of 200 cubic centimeters of 7 per cent aluminum hydroxide diluted with 600 cubic centimeters of water per twenty-four hours has been described by Woldman and Rowland[130] as providing satisfactory neutralization. Emery and Rutherford[38] used 15 cubic centimeters per hour (360 cc. per day), similarly diluted, and maintained complete neutralization. The patients treated by these authors by the drip method were shifted to the oral method at the end of a week.

X-ray Therapy.—Radiation therapy has been tried for nearly all diseases. Wilms,[127] in 1916, was the first to use it for peptic ulcer, but the largest series so treated was that of Matoni,[75] who reported complete healing of the ulcer in 77.1 per cent of 140 cases, improvement in 13.6 per cent and no improvement in 9.3 per cent. These figures must be scrutinized with the same care as all therapeutic "results." There is no evidence that irradiation *per se* will promote proliferation and healing of connective tissue or mucosa. There is evidence, however, that irradiation may inhibit gastric secretion, thus providing a rational basis for its use in the treatment of ulcer. The effect obtained varies with different persons as well as with the dose of radiation. Of 88 patients treated by Palmer and Templeton[96] with a dose of approximately 3,000 roentgens, complete but temporary histamine achlorhydria developed in 35, lasting from a few days to several months. During this phase ulcer symptoms were invariably absent. and roentgen or gastroscopic evidence of progressive healing was usually obtained. In no instance did the symptoms of ulcer recur, nor did the ulcer increase in size during the achlorhydria. Some reduction in gastric secretion in response to histamine was obtained in all cases. Permanent achlorhydria did not develop in any instance. The gastric secretion, as judged by the histamine test, returned to normal in the course of a variable number of months. Recurrent ulcers were observed after the acid gastric secretion returned. Radiation therapy is not the answer to the ulcer problem, but it is of value in certain cases, particularly for difficult duodenal ulcers and for jejunal ulcer recurrent after gastroenterostomy with or without partial gastrectomy.

Radiation may be given by various formulas. In the studies mentioned, five treatments were given anteriorly and five posteriorly on alternate days, directed at the fundus of the stomach through portals 15 centimeters square, each dose—consisting of approximately 300 roentgens—a total of 3,000 roentgens measured in air, or a depth dose of approximately 2,000 roentgens. The formula was 200 kilovolts, 25 milliamperes, 1 millimeter of copper plus 1 millimeter of aluminum filtration, a focal skin distance of 50 centimeters and a delivery of 32 to 38 roentgens per minute. In addition to the disagreeable roentgen sickness, serious complications developed in 2 cases: In one there was a localized necrosis of the left lobe of the liver (not fatal), and in the other a rather troublesome diarrhea lasted for several weeks. A second series was then treated with a smaller dose, 1,200 roentgens measured in air (depth dose, approximately 800 roentgens), consisting of three anterior and three posterior exposures to 200 roentgens each. The results were much less satisfactory, but this course can be repeated with safety one or more times. At the present time a third study is in progress, in which ten treatments of 225 roentgens each are given, five anteriorly and five posteriorly, for a total of 2,250 roentgens measured in air (depth dose, approximately 1,500 roentgens). The susceptibility of the subject to irradiation, judged by the inhibition of gastric secretion, is not correlated with the degree of roentgen sickness or with age, sex, body weight or build. It is most variable and unpredictable.

Radiation therapy should not be used to the exclusion of the antacid medication but be combined with it. The effect of the therapy on gastric secretion whould be checked with histamine every two to four weeks. Alkali may be discontinued during achlorhydria, if such develops, and given in a decreased dose during marked depression. On the whole, however, the irradiation should be incidental to the complete therapeutic program.

Hormone Therapy.—No adequate basis has existed in the past for hormone therapy in the treatment of peptic ulcer, although various preparations have been used. Atkinson and Ivy[5] observed no significant effect on gastric secretion from the administration of theelin, emmenin, pitressin and pituitrin or pepsin. Sandweiss, Saltzstein and Farbman,[108] starting with the observation that pregnancy has a beneficial effect on peptic ulcer, were unable to observe any effect on the development and course of experimental ulcer (Mann-Williamson) from the injection of estrogenic substance (theelin). They also used antuitrin-S and were somewhat encouraged by the results, but the evidence was not impressive. Culmer, Atkinson and Ivy,[32] however, observed a significant reduction in gastric secretion in Pavlov pouch dogs after the daily administration of extracts of pregnancy urine. Gray, Wieczorowski and Ivy[50] found a heat-stable substance lacking in gonadotropic activity in normal female and male urine. The chemical and biologic behavior of the substance resembles that of enterogastrone, a humoral agent prepared by Ivy and his co-workers from duodenal mucosa and shown to be capable of depressing gastric secretion and motility in the dog.[49] The substance may be similar to that found by Brunschwig, Prohaska, Clarke and Kandel[20] in the achlorhydric gastric juice of patients with pernicious anemia or gastric neoplasm and shown by them to be a powerful secretory depressant. There is thus reason to hope that a hormone of clinical value in the depression of gastric secretion and the treatment of peptic ulcer may be found.

The possible role of the pituitary gland has been emphasized by Metz and Lackey.[77] Its removal increases gastric secretion and motility, whereas the administration of posterior pituitary extract decreases both secretion and motility. They tried the effect of posterior pituitary extract on patients with ulcer, choosing the intranasal method of administration in order to avoid the disagreeable side-effects obtained with subcutaneous injections. The dose was 40 mg. snuffed four times daily, thirty minutes after each meal and at bedtime, for five to six weeks, after which half that dose was given for one or two more weeks. "Satisfactory clinical results" were obtained by patients treated by the oral or the subcutaneous route. These results were not impressive, but may warrant further consideration. Unsatisfactorily explained, however, is the production of chronic gastric ulcer in rabbits by Dodds, Hills, Noble and Williams[34] by oral and subcutaneous administration of an extract of the posterior lobe of the pituitary gland. Acute ulcers did not appear if the gastric content was rendered alkaline prior to the administration.

Mucin Therapy.—There is considerable evidence that the normal mucosa is protected from digestion by the acid gastric juice by means of a thin layer of mucus and that in patients with ulcer the mucus of the gastric juice is diminished in amount. The treatment of peptic ulcer with mucin with favorable results has been reported.[4] The reports in the literature are contradictory. Orndorff, Fauley and Ivy[84] found mucin to have rather definite value in the prevention of experimental ulcer in Mann-Williamson dogs, but mucin alone to be less effective than mucin with alkali and raw ground pancreas. Brown and Dolkart[18] apparently prefer mucin therapy to other forms of treatment. As a protein, mucin possesses definite ability to neutralize acid, but there is little reason to think that it is superior to other proteins or that it actually "coats the ulcer." Mucin is rather disagreeable to take, but its use may be included in the ulcer management program outlined if desired.

Foreign Protein Therapy.—There is little, if any, rational basis for foreign protein or other "injection" treatments of peptic ulcer, except for psychotherapeutic reasons, as illustrated by the "excellent results" obtained by Sandweiss after the intravenous injection of distilled water. Fever does produce a transitory decrease in gastric secretion, but it is scarcely sufficient to be significant.

Removal of Foci of Infection.—Acute ulcers and erosions are not infrequently found at autopsy in the presence of acute infectious diseases, but neither this fact nor the demonstration of foci of infection in persons with ulcer proves an etiologic relation between the chronic foci of infection and the ulcer. Such foci should be treated for local reasons. A remission of the symptoms of ulcer may follow such therapy, but again there is no evidence that the relation is causal.

Medical Treatment of Massive Hemorrhage.—**Starvation.**—The time-honored regimen of treatment of massive hemorrhage is bed rest, elevation of the foot of the bed, application of an ice bag to the epigastrium, giving of morphine in doses adequate to quiet the restlessness and complete deprivation of food and drink for one to three or four days. In many cases this procedure is the one of choice.

Meulengracht[78] Regimen.—In recent years the frequent feeding program of Meulengracht has received wide consideration. It is superior to the old procedures of starvation and "skilful neglect," but not superior to other measures involving immediate feeding, such as prompt institution of the Sippy schedule.

Sippy's Program of Management.—Sippy and his colleagues worked out a detailed, complete and rational scheme of neutralization, now in use for massive hemorrhage in many institutions for a number of years. The following program is based essentially on the Sippy regimen:

1. Absolute rest in bed should be maintained.

2. Restlessness should be controlled by means of subcutaneous injections of morphine, $\frac{1}{8}$, $\frac{1}{6}$ or, if necessary, $\frac{1}{4}$ grain every four hours, combined with $\frac{1}{120}$, $\frac{1}{100}$ or $\frac{1}{75}$ grain of atropine. Sodium luminal may be used to supplement or replace the morphine, but on the whole morphine is more satisfactory. It should be used unhesitatingly, although the patient should not be "snowed under."

3. The blood pressure and pulse should be watched carefully, readings being taken at half-hourly or hourly intervals. Sippy cautioned against the determination of the blood pressure during hemorrhage because of the danger of increasing the blood pressure by the sudden although temporary stopping of the circulation through the arm. This effect has not been observed, and the blood pressure reading does provide valuable information bearing on the immediate course of the hemorrhage. The blood count does not drop materially until several hours after the initial hemorrhage, because of the time required for the blood volume to be restored by the addition of tissue fluid. *Time* is thus an important consideration. It is necessary to decide whether the bleeding has just started or has been in progress for several days. Slow continued loss of blood is tolerated much better than rapid bleeding. The blood pressure and pulse are therefore better guides than the blood count.

4. Blood transfusions are extremely valuable, although this point is not universally admitted. The patient's blood type should be determined at once and a compatible donor found, in order that transfusion may be performed promptly if it is needed. Meticulous attention must be given to the matching of the blood, for reactions are highly undesirable. Great care must be exercised also in the technic of transfusion. The blood should be injected slowly, at the rate of 2 to 4 cubic centimeters per minute. The preliminary saline solution should be limited to 50 to 100 cubic centimeters and a similar small amount be allowed to flow into the vein after the blood.

Transfusion is indicated when the pulse rate exceeds 120 per minute and when the blood pressure drops below 100 mm. of mercury, unless it immediately rises. Under such circumstances the patient usually appears anxious and restless. If the bleeding has been in progress for a number of hours, the erythrocyte and the hemoglobin level may be low and yet the pulse rate and blood pressure be within the critical range described. Transfusion is, as a rule, indicated if the red cell count is below 3,000,000 per cubic centimeter; the lower the count, the greater is the indication. When the erythrocyte level is below 2,000,000, a relatively small hemorrhage may be fatal. The amount of blood to be given is perhaps a matter of opinion. The general tendency is to use 500 or 600 cubic centimeters. The alleged basis for the use of smaller amounts is not convincing, and the results obtained with the larger volumes seem satisfactory. Repeated transfusions may be required when the condition is severe, perhaps eight or ten being given in the course of a week; but the greater the number of the transfusions necessary, the graver the outlook, not because the transfusions are harmful, but because the presence of a large and probably sclerotic bleeding artery is thus indicated. In such cases the need for ligation is apparent, and yet by the time the indication is evident the operative risk has become poor and every one is reluctant to undertake surgical intervention.

5. If vomiting is present, starvation is indicated only until the nausea and vomiting have completely subsided and the patient desires food. During this period of fasting, lasting for several hours or perhaps one or more days, the dryness of the mouth may be relieved with cracked ice, although the patient should be instructed not to swallow the water and saliva. Physiologic solution of sodium chloride with or without 5 per cent dextrose may be administered subcutaneously in amounts of 1,000 to 1,500 cubic centimeters per day. Large amounts are best withheld; the intravenous method of administration should not be used. Moderate dehydration is desirable, because low blood volume and low blood pressure presumably favor coagulation. In certain cases of hemorrhage from known duodenal ulcer, continuous aspiration of the stomach has proved beneficial. The amounts of acid gastric juice obtained are surprisingly large, and the loss of chloride thus induced may result in alkalosis unless it is replaced parenterally.

If vomiting is not present, food, liquid and antacids should be given at once. Sippy advised the initial administration of 4 Gm. of magnesium oxide and 2 Gm. of calcium carbonate in 1 or 2 ounces of water, followed half an hour later by the same dose or by 2 Gm. each of calcium carbonate and magnesium oxide. Calcium carbonate in 2 Gm. doses was then to be given every half hour for ten or twelve hours, followed by 4 Gm. hourly for another eight to ten hours. The following day 1.3 Gm. of calcium carbonate was recommended at half-hour intervals and during the night 2.7 Gm. at one hour intervals. Routine management could usually be instituted by the third day. This program is well calculated to neutralize the acid, but the initial laxative effect of the magnesium oxide seems excessive, and there may be difficulty with fecal concretions resulting from the large doses of calcium given after the initial magnesium oxide. It is fully as satisfactory to proceed at once with the usual milk and cream and powder program with certain modifications.

Equal parts of milk and cream or, if preferred, whole milk may be given hourly from 7 A.M. to 9 P.M. in amounts varying from 30 to 120 cubic centimeters—usually the customary 90 cubic centimeters. Sodium chloride may be added to the milk in amounts of 3 to 5 Gm. per liter and, if alkalosis is suspected, may be given in pill form in additional amounts of 5 to 15 Gm. daily. Calcium carbonate in doses of 2 to 4 Gm. with 60 or 90 cubic centimeters of water is given hourly from 7:30 A.M. to 9:30 P.M. or combined with the milk and cream on the hour. The aspiration of the stomach is omitted and the administration of milk and cream together with 4 Gm. of calcium carbonate continued through the night, at 10 P.M., midnight and 2, 4 and 6 A.M., the patient being awakened if necessary. Sufficient powders of magnesium carbonate (2 Gm.), usually two to five per day, must be substituted for the calcium carbonate to *prevent rectal impactions*. This medication is continued until the stools have shown no occult blood for two or three days. Roentgenologic and often gastroscopic examinations are then in order, to determine, if possible, the location of the lesion and the complications present. Aspiration of the stomach may then be carried out safely and the customary routine of ulcer management followed. The further therapy depends, of course, on the conditions found. If the bleeding, as evidenced by the presence of occult blood in the stool, does not cease in two or three weeks, and if the patient is in good condition, *x*-ray examination should not be further deferred. The risk is small, and a careful brief examination may disclose the very important information that the bleeding lesion is not a benign ulcer but a frank neoplasm or perhaps esophageal varices.

Drip Methods.—The drip methods possess certain advantages in the treatment of massive hemorrhage, particularly more constant neutralization of the acid. The disadvantages are the fact that the presence of the tube in the posterior nasopharynx may induce emesis in a person already slightly nauseated and the possible predisposition to pulmonary infection previously mentioned.

Vitamin Therapy.—The recognized importance of ascorbic acid for the bleeding of scurvy has led in recent years to the extensive use of vitamin C in the treatment of bleeding ulcer. Chamberlin and Perkin[26] did find that hospitalized patients on ulcer management have lower levels of ascorbic acid in the blood and urine than normal persons, but they found no clinical evidence that administration of the preparation is of any value in the treatment of patients with peptic ulcer with or without hemorrhage. There seems no reason to incriminate any other vitamin, known or unknown.

Use of Blood Coagulants.—Numerous attempts have been made to promote coagulation with substances such as thromboplastin, without definite success. Possibly some suitable product will be discovered, but at present the outlook is not very encouraging. Steinberg and Brown[118] have shown the powerful blood-coagulating properties of oxalic acid injected intravenously, but the initial experiences have as yet not been very heartening.

Indications for surgical treatment are discussed elsewhere in this book. (Chapter X.)

Results of Treatment of Peptic Ulcer.—Statistical evaluation of the results obtained is of little value, for the results depend on the location and size of the lesion—together with the complications present; on the patient's willingness and ability to coöperate, and on the physician's knowledge, personality, tact, enthusiasm, persistence, resourcefulness and painstaking care in the management of the case at hand. As a rule, however, the treatment of ulcer may be undertaken with cautious confidence regarding both the initial lesion and the prevention of recurrences. In few chronic diseases are the results more definite or more gratifying.

Peptic Ulcer and Military Service.—Dyspepsia has doubtless been a major problem in all armies in all wars, but not until the present conflict has the real incidence of peptic ulcer been recognized.[90] The enormous development of roentgenology in the past three decades is primarily responsible for the change. In 1940 Payne and Newmann,[98] in a careful study of 287 patients with dyspepsia, found 226 with proved peptic ulcer and 21 with probable ulcer. Urquhart, Singleton and Feasby[123] stated that 21 per cent of 839 soldiers returned to Canada for medical reasons were invalided because of peptic ulcer. Chamberlin[25] reported that patients with peptic ulcer constituted approximately one-third of the patients on the gastrointestinal service of the Lawson General Hospital, and Berk[13] found them to comprise 43 per cent of those on a similar service at the Tilton General Hospital. Rush,[105] in describing his first year's experience in the South Pacific close to the combat zone, noted that peptic ulcer was diagnosed in slightly over 1 per cent of all medical patients (19 per cent of all patients admitted for treatment of disorders of the upper part of the gastrointestinal tract). Of particular interest is Rush's observation that Army general classification tests of patients with peptic ulcer indicated no significant deviation from normal. Payne and Newman[98] found—and other authors have in the main corroborated the observation—that 92 per cent of the ulcers have been present before the war. Psychologic factors did not seem to have played as important a role as the dietary. In military service it is not possible to follow a soft diet or frequent feeding regimen, and patients with ulcer simply do not tolerate the normal schedule of three square meals a day. There seems to be almost complete unanimity that men with peptic ulcer do not belong in the armed forces; that they should not be admitted, and that they should be discharged when the condition is found (Chamberlin,[25] Wade,[125] Logan and Bransford[71]).

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CHAPTER X

INDICATIONS FOR THE SURGICAL TREATMENT PEPTIC ULCER

It is now agreed by internists and surgeons that the surgical treatment of peptic ulcer is in reality confined to its complications. From the standpoint of therapy, use of the term peptic ulcer to include duodenal as well as gastric ulcers is unfortunate, since treatment may be different for the two types.

Duodenal ulcer is much more common than gastric ulcer. The incidence of 78 per cent duodenal ulcer encountered roentgenologically by McMullen[10] in 883 cases of peptic ulcer is probably a fair index of the relative frequency of the two types.

During the past several years a better understanding of the type of operation advisable for the various complications of peptic ulcer has changed the outlook on therapy, largely because the results following operation have greatly improved. In general, it has been discovered that the more conservative types of operations, including gastroenterostomy and pyloroplasty, are followed by a relatively high incidence of persistence of symptoms; unfortunately, the failures following gastroenterostomy are frequently due to jejunal ulcer, which is much worse than the original ulcer. After gastric resection, jejunal ulcer is uncommon. Although mortality rate may be somewhat higher after gastric resection than after more conservative types of operation, proper preoperative and postoperative care should reduce this rate to not more than 5 per cent, and considerably less when the patients present good risks.

The complications, which are of primary surgical interest, are extremely variable and include (1) perforation, (2) hemorrhage, (3) obstruction, (4) refractory ulcers and (5) jejunal ulcers (postoperative).

Perforation is a serious complication, requiring immediate surgical therapy. It probably accounts for more fatalities than any other compliction. It was encountered in 8 per cent of ulcer cases observed by Crile and Crile,[5] but is rare in women. Shawan[12] reported an incidence of only 2 per cent in women in his series. Although in his cases the ulcer was in the duodenum in 59 per cent, in the pylorus in 15 per cent and higher up in the body of the stomach in 26 per cent, a comparison of these figures with the incidence of duodenal and gastric ulcer really indicates that perforation is a more frequent complication of gastric than of duodenal ulcer. More perforations of duodenal ulcer are encountered merely because more duodenal ulcers exist.

About 25 per cent of patients with perforation give no history of ulcer. The majority, however, do have symptoms and will admit that they have not been under strict medical care. Occasionally, serious infractions in diet and drinking are important in production of the perforation.

Manifestations of perforation of a peptic ulcer are so dramatic that it should not be difficult to recognize the condition. The pain develops suddenly and is intense. Not infrequently the patient collapses when the perforation occurs. This collapse must be differentiated from true shock.

The blood pressure is usually normal and the pulse elevated only slightly, contrasted to the low blood pressure and fast pulse with surgical shock. However, the patient may be ashen gray and covered with a cold sweat as with surgical shock. Almost immediately the abdominal muscles become rigid, particularly those in the upper part. Nausea and retching are nearly universal, but vomiting may be a late symptom. To some extent the time elapsing since eating the last meal will determine the amount of vomiting; if perforation occurs shortly after a meal, vomiting is apt to occur early. The pain is so intense that the patient usually lies with his body flexed and his hands over his abdomen.

After an hour or two the pain decreases somewhat, but the muscle spasm remains. The body may become warm, and the skin may regain its normal color. As a matter of fact, the patient appears to be a better operative risk at this time than when seen immediately after the perforation.

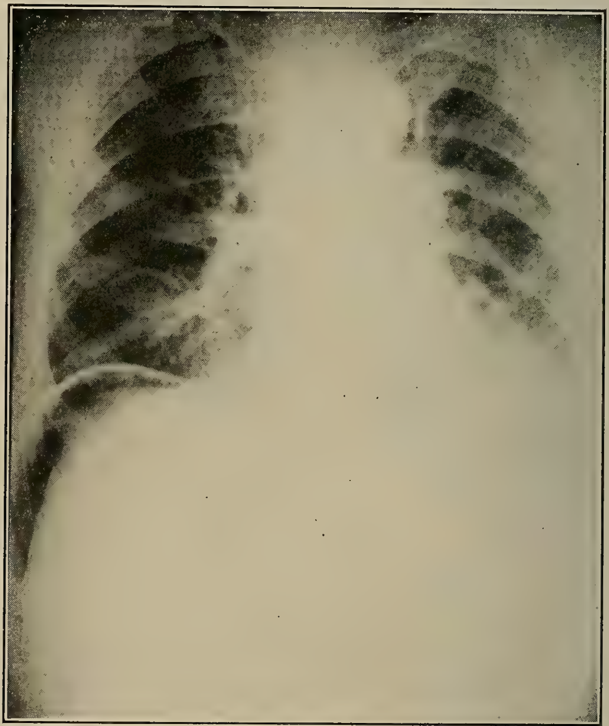

Fig. 55.—Gas under the diaphragm following perforation of a duodenal ulcer.

The patient's condition changes rather rapidly, so that at the end of twelve hours his pulse and temperature have begun to rise. By this time the white cell count will show a sharp elevation. Slight distention will perhaps be noted. Whereas the peritoneal irritation at the time of perforation was largely chemical, it is now becoming bacterial. In other words, a general peritonitis is developing.

At the end of twenty-four hours, distention becomes more pronounced, and the pulse and temperature continue to rise. It may be extremely difficult to decide whether operation is advisable when the patient is seen late with these manifestations. In general, the mortality rate increases in direct proportion to the time since perforation. For example, the mortality rate following laparotomy in a patient seen forty-eight hours after an open perforation is usually so high (over 50 per cent) that operation is not advisable. It is better to treat the patient conservatively, hoping that a walling-off process will limit the infection. However, I firmly believe that patients seen twenty-four hours after perforation may still be operated on and will do better under operative than under conservative treatment, particularly since the advent of sulfonamides. Most of the fatalities are related to infection, *i. e.*, extension of the peritonitis; the antibacterial action of the sulfonamides has lowered the mortality rate in this group (*i. e.*, those seen twenty-four hours after perforation) to such an extent that operation is justifiable.

Diagnosis is confirmed by the air bubble under the diaphragm demonstrable by *x*-ray. On the other hand, failure to find an air bubble does not eliminate perforated ulcer.

Perforations may be *subacute* or *chronic*, when there may be little or no spillage of intestinal contents. Practically all acute perforations occur on the anterior surface of the duodenum or pylorus, whereas most subacute and chronic perforations occur on the posterior wall of the duodenum and the lesser curvature or posterior wall of the stomach, possibly extending into the liver and various other structures with the formation of small abscesses. Diagnosis may be difficult. Pain is severe, but muscle spasm is usually insignificant. With few exceptions operation will likewise be indicated for this type of perforation.

The chronic types of perforation are not to be confused with the *formes frustes*, which in reality are free into the peritoneal cavity, but seal over spontaneously with omentum or adjacent organs. This type of perforation is no doubt more common than has been realized, since the spontaneous closure will result in rapid subsidence of symptoms. Advisability of operation here depends entirely on the local signs. If the patient still retains muscle spasm with severe pain, operation will usually be indicated. On the other hand, if the local signs have largely disappeared, conservative treatment, at least for a time, may be entirely safe even though the symptoms and onset were suggestive of perforation into the free peritoneal cavity.

Hemorrhage.—From the standpoint of treatment, acute massive hemorrhage is one of the most difficult complications encountered in peptic ulcer. The chief difficulty lies in the decision as to operation. The mere fact that each side of the question has competent supporters suggests that neither has a striking advantage. Hemorrhage is more common from duodenal than from gastric ulcers. Serious hemorrhage is more likely to occur from the posterior duodenal wall, where it is relatively inaccessible.

The difference between recurrent mild hemorrhage and acute *massive* hemorrhage should be sharply emphasized. Much of the confusion in the literature regarding therapy and results is dependent on the failure of authors to distinguish the two. Absolute discrimination is essential, since the mortality is high for acute massive hemorrhage and is low for mild recurrent hemorrhage. Fortunately, the mild hemorrhages are much the more common. Thorstad[14] estimated that though 18 to 20 per cent of peptic ulcers bleed, acute massive hemorrhage develops in less than 1 per cent. *Only* patients who bleed to *shock* or have a red blood cell count of less than 3,000,000 following a single hemorrhage should be considered as having had acute massive hemorrhage.

The most significant reasons for discriminating between the two types of hemorrhage lie in the vast difference in mortality and in the type of treatment. For example, Walters and Cleveland[16] reported a mortality of only 4.1 per cent in 119 cases of bleeding peptic ulcer following gastric resection; but this report included all types of hemorrhage, most of them mild, and the authors expressed the opinion that in 33 per cent of cases of massive hemorrhage after age forty-five death will occur, particularly if treatment is expectant.

This exceedingly high mortality rate led Finsterer[7] to resort to surgical measures for the control of hemorrhage. His results were so striking as to be scarcely convincing. However, it seemed clear from his results that if operation is to be performed, it must be done within the first forty-eight hours after onset of hemorrhage. In 78 patients operated on within forty-eight hours, the mortality rate was 5.1 per cent, compared with 29.7 per cent for 74 patients operated on later. His figures in the first group were almost utopian, and have not been equaled by other surgeons. Gordon-Taylor[8] had a mortality rate of 19 per cent in a series of patients with acute massive hemorrhage treated under similar circumstances, about the average surgical results for this condition.

Numerous studies have been made in an endeavor to determine what method of treatment is advisable. In a summary of cases collected from numerous clinics, Bohrer[4] found a mortality rate of 14.5 per cent in 55 cases of duodenal ulcer operated on for massive hemorrhage, compared to 22 per cent in 199 cases when treatment was conservative.

Thorstad[14] reported mortality of 2.8 per cent in 70 cases when treatment was by prompt feeding: 13.7 per cent in 38 cases, by starvation, and 14 per cent in 7 cases, by operation. He also noted that only 3 patients who had had a previous history of hemorrhage died. Of 18 other patients who died there was no history of previous attacks of hemorrhage. From this observation alone it might appear that if the patient has a history of chronic hemorrhage, the immediate result will be favorable, and radical procedures need not be considered. Thorstad stated that death does not follow the initial hemorrhage bu results from successive hemorrhages over a few days.

It is readily discernible that there is no agreement as to the type of therapy advisable for acute massive hemorrhage. I am not convinced that acute massive hemorrhage should always be submitted to operation, although I have seen 2 patients (under forty) die after conservative management. In any event, if operation is to be performed, *it must be within the first forty-eight hours,* and not after successive hemorrhages, when the mortality rate prohibits consideration of surgery. Again I wish to emphasize that sharp discrimination must be made between mild hemorrhage and acute massive hemorrhage. Physicians who report no deaths in a significant series of patients bleeding from peptic ulcer have been fortunate in not having had many cases of massive hemorrhage. In other words, the mortality rate in massive hemorrhage will be high (*i. e.,* 20 to 30 per cent) regardless of the method of therapy.*

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* This type of hemorrhage is one of the most frustrating for the phsyician. In my experience early surgical intervention for a ruptured pancreaticoduodenal artery offers the patient a better outlook than the most scientific medical management.—EDITOR

Obstruction.—When ulceration has been present over an extended period, the resultant fibrosis may cause obstruction to the lumen, usually to that of the duodenum because that of the pylorus is much larger. In general, obstructions in the pylorus are likely to be malignant, while those in the duodenum are practically always benign. Allen and Welch[3] noted that about one-fourth of operations for duodenal ulcer were for obstruction, an incidence about equal to that for perforation.

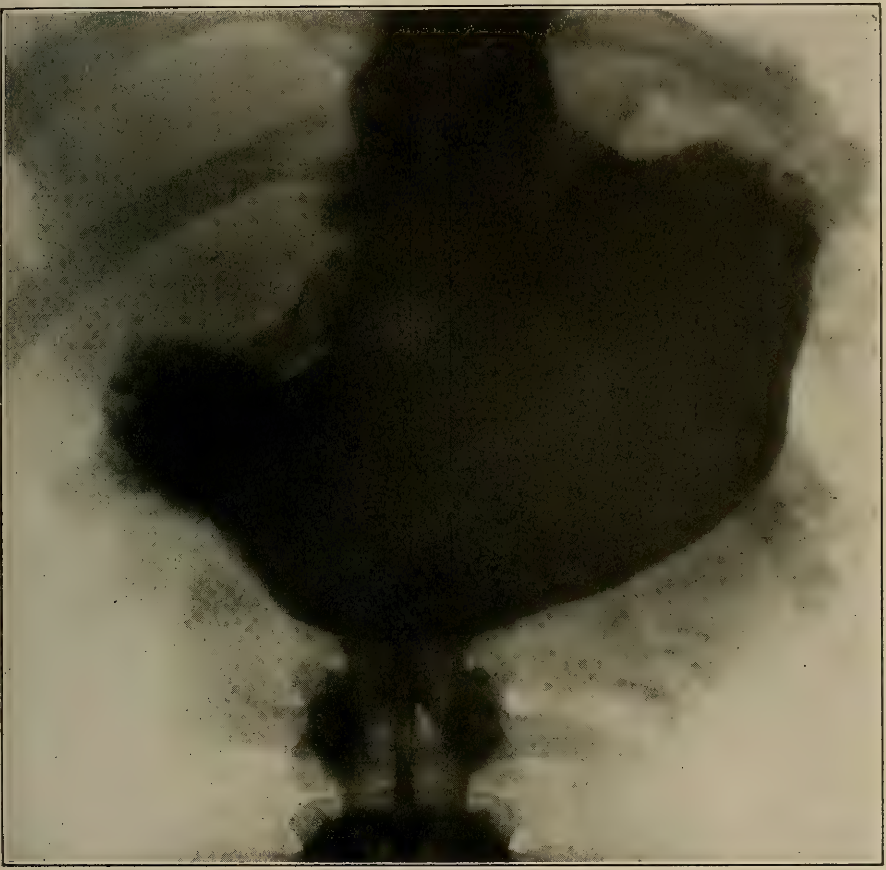

FIG. 56.—Six-hour film showing severe obstruction. The patient vomited only two or three times per week, owing largely to the fact that the intake had gradually been decreased to only a fraction of normal requirements.

The clinical manifestations of duodenal obstruction are fairly characteristic, but differ sharply from the manifestations produced by the ulcer itself. By careful questioning, the physician can readily determine when the obstruction started. This is, of course, important, since it determines to a great extent the urgency of operation. Typical of duodenal ulcer are relief of distress following meals or administration of alkalis such as sodium bicarbonate. When significant obstruction develops, intake of food or alkalis will not relieve but will increase distress. As a matter of fact, nausea may develop after meals, and as the obstruction increases, vomiting will appear. However, there usually is surprisingly little vomiting considering the degree of obstruction shown by x-ray (Fig. 56). I have seen almost complete duodenal obstruction with a history of vomiting no more frequent than once a week, largely because the patient has insidiously cut down his intake of food and water to a great extent.

One of the first duties of the physician after admission of the patient to the hospital is to determine the degree of obstruction. This is done largely by roentgen study, but aspiration of the stomach four to six hours after a meal will give valuable information. From the standpoint of therapy it is essential that the physician differentiate obstruction due to fibrous stenosis from pylorospasm. This usually is not difficult, and the history itself may make the differentiation. For example, if a patient has been progressing satisfactorily with few or no symptoms on a certain ulcer regimen but suddenly has severe epigastric distress with nausea and vomiting following a Saturday night debauch, it will be obvious that pylorospasm is the cause. Adequate medical treatment will restore the patient to his previous status. But if the symptoms of obstruction have developed insidiously and progressively without any history of acute over-indulgence, the diagnosis of obstruction due to stenosis will be fairly conclusive.

Treatment for pylorospasm is obviously medical, and treatment for organic obstruction is usually surgical. Although patients with organic obstruction can be carried along under medical treatment satisfactorily for some time, it is in general not wise to do so, since obstruction not associated with pylorospasm will gradually become more severe. It is obvious that the mortality rate and postoperative convalescence will be much better when obstruction is of short duration.

Time of operation is extremely important and is given insufficient thought by most physicians and surgeons. The aim of the physician as well as the surgeon is to pare the mortality rate down to the lowest possible figure. The medical profession learned during the past decade that pre- and postoperative care are exceedingly important in maintaining low mortality rates. In other words, the patient must be in the optimum physical condition at the time of operation. The preoperative treatment, particularly from the standpoint of duration, varies greatly, depending on the degree of obstruction. If the obstruction is such that even with hospital care the patient is able to take and assimilate no more than a few hundred calories per day, delay in operation beyond a certain point is highly undesirable. The first obligation of the physician is to correct dehydration and electrolytic imbalance. At the same time he must force caloric intake (oral and parenteral) to the maximum. Intravenous administration of 5 or 10 per cent dextrose and aminoacids is extremely important. Naturally, heavy vitamin therapy, including vitamins A, B, C and D, is likewise instituted. If obstruction is fairly complete, vitamin therapy will have to be parenteral and confined to B and C, which in reality are the most important. If the oral intake is no more than a few hundred calories, the amount of calories gained by intravenous administration of dextrose and aminoacids will not be sufficient to produce a significant gain in weight, or improve the patient's physical condition. Therefore, operation is usually desirable in from forty-eight to seventy-two hours, the time required to correct fluid and electrolytic imbalance, which is important.

If the obstruction is only partial and the patient is able to take an assimilate daily 1,000 or more calories by mouth, the supplementary administration of dextrose and aminoacids intravenously will continue to improve the patient's condition from day to day, and will result in a gain in weight. Operation in such cases may profitably be delayed for ten days or more for correction of vitamin imbalance. However, careful check on the patient's weight and the amount of gastric retention must be made, lest the physician be misled as to the caloric intake and assimilation.

The type of operation for duodenal obstruction is extremely important in the results obtained, and will vary in each individual case. In general, massive resection is unwise in the presence of fairly complete obstruction anywhere in the intestinal tract. However, my experience and that of many other surgeons indicate that resection of the stomach can be done safely in the presence of a fairly complete obstruction, when preoperative and postoperative care are good. As stated previously, the operation which is followed by the lowest incidence of persistence of symptoms or jejunal ulcers is gastric resection. In general, jejunal ulceration follows an operative procedure when hyperacidity has not been corrected. In some cases of obstruction the acidity will be diminished to a normal or slightly subnormal level. In these, gastroenterostomy will be followed by good results, particularly if a long stoma is made in the most dependent portion of the stomach. If the patient's physical condition is poor, this operation may be preferable to gastric resection.

I am convinced, with Wangensteen,[18] Allen[1] and others, that removal of the duodenal ulcer is not necessary, providing the pyloric mucosa is excised. When the ulceration extends over a large area in the duodenum, excision will make a satisfactory closure of the duodenal stump impossible. Since the most serious operative complication (from the standpoint of mortality) is leakage of the duodenal stump, this factor becomes important. By leaving about an inch of pylorus and excising its mucosa, which is extremely simple, good closure can be obtained, and the risk of duodenal leak obviated.

Gastric Ulcer.—Tremendous responsibility rests on the shoulders of the physician who treats gastric ulcer medically, because of the danger of carcinoma, either as a primary tumor or as a secondary growth. Gastric carcinoma is so invasive that a delay of a few months will usually be disastrous from the standpoint of a five- or ten-year cure. Medical treatment of gastric ulcer is satisfactory, but even an occasional error of treating a malignant ulcer as benign is not to be condoned, since it can be prevented by resection.*

Unfortunately, accurate differential diagnosis between benign and malignant ulceration of the stomach is extremely difficult. Though gastric ulcer on the lesser curvature in a patient twenty-five years of age is likely to be benign, gastric ulcer in a patient in the cancer age may be malignant regardless of its location. Ulcers along the greater curvature are usually malignant, and ulcers larger than a quarter or half dollar are generally malignant. Ulcers under this size may be benign, but it must be remembered that all malignant tumors start as small lesions. The difficulty of accurate diagnosis has been emphasized by Steigmann[13] and Walters.[15] Walters reported that in 10 per cent of the cases in his series carcinoma had been diagnosed preoperatively as benign ulcer. Further, 30 per cent of the gastric cancers had an ulcer type of history, and of this group 80 per cent had responded to medical treatment. Ordinarily, achlorhydria is considered a fairly accurate indication of the presence of carcinoma. However Walters noted that "a relative achlorhydria was present in only 51.4 per cent of the cases of gastric cancer in which resection was performed." Furthermore, free hydrochloric acid "ranged from 1 to 29 in approximately 30 per cent, from 30 to 49 in approximately 15 per cent, and 50 degrees or over in approximately 5 per cent of the cases, respectively."

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* It is my personal belief that all gastric ulcers in patients of carcinomatous age are better off in the hands of a capable surgeon. Medical procrastination may lead to disastrous results. —EDITOR.

Eusterman[6] emphasized that small ulcerating carcinomas may respond so well to medical treatment as to give the impression roentgenologically that they are benign.

In summary, the physician must be *positive* of his diagnosis when adopting conservative treatment. The results of gastrectomy for gastric ulcer are so satisfactory and associated with such a low mortality rate that resection for a doubtful ulcer which turns out to be benign microscopically is not at all a serious error. For example, in his large experience Walters reported that he had never seen a recurrent ulceration in a patient having had half or more of his stomach resected for a gastric ulcer. Opinions differ somewhat as to the incidence of carcinomatous change in gastric ulcers. I concur in the opinion of Walton,[17] a competent authority on the subject, that about 10 per cent of gastric ulcers become malignant in time.

Refractory Ulcer.—Fortunately, most duodenal ulcers respond to medical treatment. In a small group, however, symptoms persist regardless of adequate therapy, even though no such complications as obstruction and hemorrhage exist. Surgeons and internists alike are reluctant to accept responsibility in such cases, since all types of treatment generally are unsatisfactory. Operation should not be done until the various possibilities of medical treatment have been exhausted. Likewise it must be established that the symptoms are due to the ulcer and not to some other disease or to neurotic tendencies.

Surgical measures, if finally decided on, must be extremely radical. Pyloroplasty, gastroenterostomy and the like are hopelessly inadequate and make a bad situation worse. Gastrectomy in such cases should include at least two-thirds of the stomach.

Jejunal Ulcer.—One of the most common causes of poor results related to gastric surgery is the development of a jejunal ulcer at the stoma. It is well known, however, that jejunal ulcers commonly follow the palliative type of operations (*e. g.*, gastroenterostomy). For this reason gastroenterostomy is being abandoned as a palliative measure for ulcer, particularly when the gastric acidity is high. With the proper type of gastrectomy (removing one-half to two-thirds of the stomach), jejunal ulcer is extremely rare. Indeed, I have never seen a jejunal ulcer following gastrectomy, but this may be somewhat of a coincidence. Allen[2] reported no jejunal ulcers following 76 gastric resections performed in thirty-four months.

Palmer[11] aptly emphasized that jejunal ulcer responds much less readily to medical therapy than does primary gastric or duodenal ulcer. It is so difficult to treat that it is usually preferable to hospitalize the patient, so that therapy may be as nearly perfect as possible. Unfortunately, perforation of jejunal ulcer is fairly common, and its symptoms are of the type of but usually more intense than those of the original ulcer. If it does not respond to medical treatment, surgical therapy is usually indicated because of the severity of symptoms. The mortality rate is surprisingly low considering the magnitude of the operation; it is no greater than that of gastrectomy, perhaps because only competent surgeons will attempt gastrectomy for a jejunal ulcer.

If jejunocolic fistula develops, the indication for operation is still stronger, since inanition may develop.

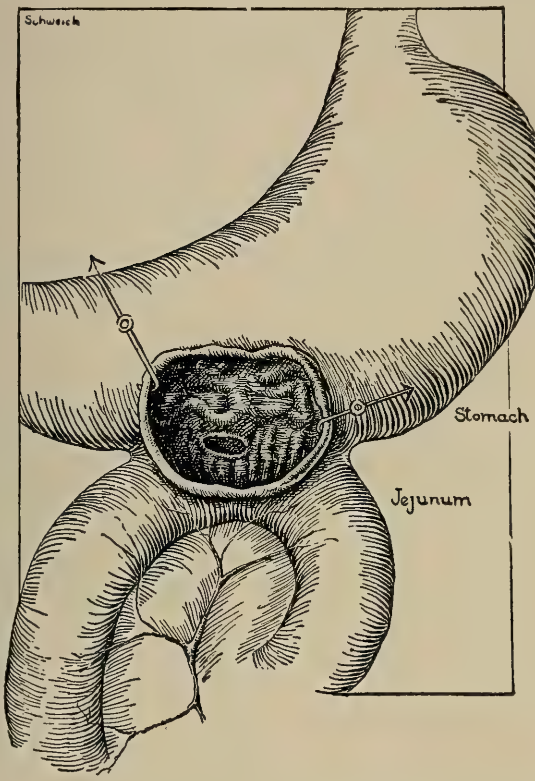

Fig. 57.—Jejunal ulcers are common complications following gastroenterostomy for duodenal ulcer. They are much less common after gastric resection, which has consequently replaced gastroenterostomy for ulcer, except on rare occasions. (From Cole and Elman, Textbook of General Surgery, courtesy of D. Appleton-Century Company.)

Relation of Mortality and Results to Surgical Indications.—In general, the decision to operate for peptic ulcer depends on four major factors: (1) the type and location of the ulcer, (2) the severity of the symptoms, (3) the clinical results to be expected and (4) the surgical risk. The indications related particularly to the type of ulcer have already been discussed. Each case in reality presents a problem of its own, since these four major features along with numerous minor ones will be different. For example, the chance of recovery for an old patient who has had a partial obstruction for months may be low. Obviously if the obstruction is complete, the operation must be performed.

The aforementioned factors are particularly important with *severe hemorrhage*. For example, if the patient is known to have an ulcer on the anterior surface of the duodenum or pylorus and a severe hemorrhage has developed, good results can be expected surgically, since the operative care of such a lesion is relatively simple. On the other hand, if there is considerable doubt as to the cause of the bleeding or if an ulcer on the posterior part of the duodenum near the sphincter of Oddi is known to be present, the surgeon may be reluctant to advise operation. The surgical treatment of an actively bleeding ulcer near the sphincter of Oddi is fraught with many hazards, and the mortality is high. Therefore, the indications for operation are less definite.

The results in *chronic* bleeding ulcers are surprisingly good, from the standpoints both of clinical results and of mortality. Walters and Cleveland[16] noted that in 87 per cent of 112 gastric resections for bleeding ulcers there was freedom from hemorrhage and further symptoms; their operative mortality for bleeding ulcers of all types was 4.1 per cent.

Many patients are too impatient or not sufficiently intelligent to carry out instructions regarding medical treatment. In fact, they frequently request operation, particularly if they believe that the chance of a cure is reasonable. From reports in the literature it now appears that the mortality following gastrectomy for peptic ulcer should be no greater than 5 to 6 per cent. In a series of 76 resections for duodenal ulcer reported by Allen and Welch[3] over three years the mortality rate was 6.5 per cent. They reported good results in all except one case, in which a stricture (traumatic) of the common duct developed. Walters[15] reported a mortality rate of 2.2 per cent in 89 cases of gastric resection during 1939, and a rate of 1.1 per cent in 88 cases during 1940. Lahey and Marshall[9] reported an operative mortality of 3.2 per cent in a series of 251 patients on whom subtotal gastric resection was performed for peptic ulcer; this represented 6.59 per cent of patients hospitalized for duodenal ulcer and 18.1 per cent of those with gastric ulcer hospitalized under their care. In my own series the mortality rate following gastric resection for peptic ulcer was 3.7 per cent (see Table). The mortality rate for carcinoma will be higher than for ulcer. Reports in the literature during the past few years vary from 8 to 15 per cent (9.7 per cent in my series).

TABLE 4.—GASTRECTOMIES (1936–1943) (Illinois Research Hospital)

	No.	Op. deaths
Carcinoma	41	4
Sarcoma	1	
Benign tumor	2	
Gastric ulcer	23	
Duodenal ulcer	25	2*
Jejunal ulcer	5	
	97	6, or 6.1%

* One death followed resection for acute massive hemorrhage.

The mortality rate after resection will be slightly higher for duodenal than for gastric ulcer, because it is more difficult to close adequately the duodenal stump when the ulcer is located in the duodenum. Naturally, the type of operation performed is important in the results to be expected. A resection which removes less than half the stomach, particularly in duodenal ulcer, is bound to be associated with a high percentage of recurrence of symptoms, perhaps including jejunal ulcer.

Numerous authorities have said that an ulcer patient is never cured, meaning that even if the ulcer is cured the patient must continue to be cautious with his diet. To a great extent this is true, but in my experience few precautions need be taken after gastrectomy. After the convalescent period,* I advise patients to eat anything they like, but to partake sparingly of raw bulky vegetables such as cucumbers and cabbage. However, all ulcer patients, whether operated on or not, should be cautioned against excessive intake of alcohol or highly seasoned food. After all, this same advice may be heeded to good advantage by persons with normal stomachs.

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* The convalescent period should be prolonged for several months. Adequate ulcer management should follow all operations. If anacidity develops, as shown by an Ewald meal, the discomfort following intake of foods may be relieved by administration of dilute hydrochloric acid. In my experience this has proved suitable to the altered physiologic picture.—Editor.

CHAPTER XI

ALKALOSIS AND ITS TREATMENT

ALKALOSIS is best defined as that disturbance in acid-base balance of the blood and other body fluids characterized by (1) an elevated carbon dioxide content or combining power of the serum and (2) a decreased hydrogen ion concentration, or an increased *p*H, of the serum. In this sense alkalosis represents an "uncompensated" state of alkali excess or acid deficit, both of which are common in clinical practice. The acid deficit is primarily in chloride. Alkalosis due to hyperventilation is a deficit of free carbonic acid. It will not be considered in this chapter because it is a special type not related to gastrointestinal diseases.

PATHOGENESIS

Excessive Intake of Alkali.—This was the most frequent cause of alkalosis when the Sippy method was the prevailing medical treatment of peptic ulcer. Ordinarily sodium bicarbonate was the alkalinizing agent; its ready solubility in body fluids explained its effectiveness in disturbing the normal acid-base balance. Calcium carbonate also produces alkalosis, possibly through the absorption of the carbonate ion, while the calcium ion is largely excreted in the feces. However, loss of chloride seems to be the chief factor in the alkalosis induced by calcium carbonate (Kirsner). The ingestion of adequate amounts of sodium acetate, citrate or lactate can result in alkalosis, because of the metabolic change of the organic acid anions to bicarbonate. Potassium salts would behave similarly to the sodium compounds, but because of their other effects could scarcely be ingested in quantities sufficient to cause alkalosis. They are, therefore, of no clinical importance in this respect.

Excessive Loss of Acid.—Gastric juice is the only body fluid to contain a strong mineral acid in a free form. Therefore, loss of acid gastric juice, whether by vomiting or by therapeutic aspiration, can result in severe alkalosis because of the unbalanced removal of chloride ion from the blood. The sodium normally equivalent to this chloride is now available for the ubiquitous bicarbonate ion, with the result that the serum bicarbonate, and therefore the serum *p*H, increases sharply. This type of alkalosis differs from that due to excessive ingestion of alkali in that dehydration is a frequent complication. In most other respects the two conditions are essentially similar clinically, the common denominator being hypochloremia.

PATHOLOGIC PHYSIOLOGY

Chemical Changes in the Blood.*—The characteristic chemical changes of alkalosis are increased carbon dioxide or bicarbonate in the serum, increased *p*H or alkalinity and decreased chloride concentration. These changes are, of course, reflected in all the extracellular or interstitial body fluids in equilibrium with the blood. Ordinarily as the bicarbonate concentration increases, the chloride concentration decreases reciprocally, so that the sum of bicarbonate and chloride remains at approximately the normal figure—125 to 135 milliequivalents per liter of serum. Since these two anions normally make up about 85 per cent of the total acid in the plasma or serum, their sum will roughly reflect the total base or cations in the serum, chiefly sodium. One would expect, therefore, and one actually finds, that the serum sodium and total base concentrations are within the normal range in simple alkalosis, provided renal function and fluid intake are adequate.

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* Throughout this chapter reference will be made to analyses of serum rather than of whole blood or ordinary plasma for electrolytes. The reason is that unless blood is drawn without stasis under oil and precautions are taken to prevent escape of carbon dioxide from the sample, shifts of chloride and bicarbonate ions readily occur between the red blood cells and the plasma or serum. Furthermore, chloride determinations on whole blood are subject to erroneous interpretation if the normal ratio of cell volume to plasma volume is disturbed by hemoconcentration or anemia. If the blood sample is properly heparinized under oil, plasma analyses will be satisfactory.

However, in alkalosis due to vomiting or other excessive loss of acid gastric juice, the associated dehydration involves a loss of sodium from the body fluids. Hence, some degree of base deficit develops, as shown by subnormal values for serum sodium and total base. This complication tends to prevent a worse alkalosis, because less sodium is now available to balance the increasing bicarbonate. The sum of serum chloride and bicarbonate will be less than normal under these circumstances, pointing to a decreased total base. A similar situation may arise in alkalosis due to excessive ingestion of alkali, if dehydration results from markedly diminished intake of fluids and salt or from vomiting.

Concomitant with these electrolyte changes in the blood is an increase in the nonprotein or the urea nitrogen. This is due to reduction of renal blood flow and filtration because of decrease in extracellular fluids and circulating plasma volume, secondary to loss of sodium. The degree of retention is usually moderate in simple alkalosis, values twice normal being found. However, in cases of vomiting, dehydration and oliguria the rise in nonprotein nitrogen is much more marked, and a uremic level is often reached. At this point, retention of acid metabolites, because of severe renal insufficiency, may cause a reduction in the elevated serum bicarbonate and *p*H. This apparent chemical improvement of the alkalosis is, however, only a misleading by-product of the critical phase of decreasing kidney function. The changes in the blood nonprotein nitrogen tend to lag a day or two behind the serum electrolyte changes in both the ascending and the descending phase of the state of alkalosis. This must be taken into account in evaluating relative discrepancies between the levels of nonprotein nitrogen and of bicarbonate and *p*H.

Urinary Changes.—The kidneys play a major role in the maintenance of acid-base balance by their excretion of acid or base according to the needs of the body. Therefore, on the administration of alkalis the urine soon becomes alkaline and the excessive electrolyte is excreted. However, there is a limit to the ability of the kidneys to concentrate any given substance, and when this limit is reached further increase in excretion must depend on the possibility of increasing the urine volume. Such diuresis often entails loss of some of the sodium and chloride from the body fluids, especially when the intake of salt is limited. If for any reason renal function should become impaired, the retention of administered alkali will proceed rapidly to severe alkalosis. The added factor of diminished intake of fluids because of nausea or actual vomiting markedly aggravates the renal situation by producing oliguria and circulatory disturbances. In extreme conditions the kidneys may excrete acid urine in spite of severe general alkalosis. This is usually due to a deficit of serum sodium because of previous loss or reduced intake and is most likely to occur in alkalosis secondary to pyloric or duodenal obstruction.

The changes in the urine during alkalosis will, therefore, depend on some of the factors just outlined. Early in alkalosis secondary to bicarbonate administration in a person with normal kidneys, the urine will contain considerable bicarbonate and be alkaline to a maximum of *p*H 8. The amount of chloride in the urine will be low, reflecting the reduced level of serum chloride. This phase of alkalosis has not been sufficiently studied clinically. The urine volume will be increased early because of the extra water taken with the alkaline powders. However, in later stages, and especially in alkalosis due to vomiting, oliguria is the rule. The specific gravity will fluctuate inversely with the volume at first, but as renal impairment increases it will become fixed at a rather low level. The combination of oliguria and a low specific gravity, below 1.018, is an indication of serious renal insufficiency. Therapeutic infusion of fluids will alter the picture, depending on the nature of the injected solution.

Albuminuria may occur, but is usually slight. It is probable that traces of albumin are often overlooked in strongly alkaline urine because of failure to acidify the specimen sufficiently. Casts and red blood cells are infrequent; even if passed, they would rapidly dissolve in the alkaline urine. The presence of albumin and formed elements in any appreciable amount speaks strongly for preëxisting renal disease unless the patient is in extreme alkalosis, with an acid urine, or is severely dehydrated.

Impairment of Renal Function.—A regular occurrence in clinical alkalosis is diminished renal function. If alkali is given after this stage, alkalosis will increase to a degree of severity dependent on the decrease in renal function. However, it is wrong to conclude that alkalosis is due primarily to impaired renal function. The change in renal function, demonstrable by the phenolphthalein test or urea clearance, lags behind the serum electrolyte changes. Ordinarily, the urea clearance will fall from a normal level to about 30 or 40 per cent of normal. If kidney function is low to begin with, further decrease will occur, with more rapid retention of nonprotein nitrogen. The azotemia of alkalosis, whether clinical or experimental, is not the result of severe hypochloremia *per se,* but rather the effect of rapid dehydration, however produced, of the extracellular fluids (Gamble; Kirsner, *et al.*). The mechanism of the effect of alkalosis on renal function is complex, although a decreased renal blood flow must be the immediate factor. Certainly morphologic renal changes are absent or insignificant in ordinary alkalosis. Another mystery is the reason for the prolonged return of kidney function to normal in some patients whose blood electrolytes have been restored to their original physiologic level. It becomes important, therefore, for the physician who administers alkalis to determine the renal function prior to, as well as during, the development of alkalosis.

Effects on the Central Nervous System.—From the clinical standpoint, alkalosis inflicts its greatest damage on the functions of the central nervous system—hence the early distaste for food, weakness, nausea and vomiting, drowsiness and mental clouding and, in the more advanced stages, stupor, twitchings and coma. Some of the later disturbances may well be due to dehydration and others to renal insufficiency. The importance of early recognition of the syndrome of alkalosis lies in the fact that the condition is easily reversible at this stage, but later on it may end in fatal coma in spite of treatment to the point of achieving normal serum bicarbonate and chloride levels and *p*H.

Although one might expect derangement of the respiratory and vasomotor centers in alkalosis, clinically it is difficult to demonstrate any clear-cut effects. Furthermore, in contrast to the effect of respiratory alkalosis in producing tetanic seizures, the alkalosis in the ulcer patient is rarely associated with neuromuscular irritability of this degree.

CLINICAL SYMPTOMS

The syndrome of alkalosis is by and large uniform, regardless of the underlying cause. This statement does not refer to the brief disturbance in acid-base balance and central nervous function produced by hyperventilation. For the sake of convenience one may classify the symptoms of alkalosis as gastrointestinal, nervous and mental, renal and blood chemical. It is obvious from what has already been stated that this division does not imply any definite order of development or importance. Many of the symptoms may arise concurrently, and there is the usual variation from patient to patient.

Gastrointestinal Symptoms.—During the medical management of peptic ulcer, particularly by the milk and cream and alkaline powder regimen, alkalosis should be suspected as soon as the patient begins to complain of a distaste for the milk and cream or powders. There are usually no actual abdominal distress or other definite gastrointestinal symptoms at this time. A change in the dietary regimen may help temporarily, but if the alkalosis continues the patient will soon lose his desire for any food and suffer from nausea and even vomiting.

In the patient whose alkalosis was initiated by obstructive vomiting due to gastric or duodenal lesions, or the one with excessive aspiration of gastric contents preoperatively or postoperatively, the gastrointestinal symptoms of alkalosis will generally be submerged in the more conspicuous clinical signs of the underlying obstructive lesion. Hence it is easy to overlook the early stages of alkalosis in this group unless one is always aware of the possibility and avails oneself of the aid of blood chemistry. Careful examination of the patient will reveal some evidence of dehydration, in the form of dryness of the tongue and diminished salivary secretion. Loss of acid gastric juice sufficient to produce some dehydration is also capable of causing alkalosis.

Gastroduodenal hemorrhage when treated with alkalis is frequently complicated by unrecognized alkalosis. Here, again, several factors militate against an early diagnosis of alkalosis. The patient is usually under sedatives; food is withheld, and large amounts of alkali are often given. Under these circumstances, gastrointestinal symptoms may not reach the complaint level or may be easily attributed to the underlying disease. It is probably for these reasons that the milder phases of alkalosis are not correctly interpreted. Hence there is a general impression that hemorrhage predisposes to severe alkalosis.

Nervous and Mental Symptoms.—Weakness is an early manifestation of alkalosis, particularly when calcium carbonate is being used. Headache, occipital or vertical, and dizziness are common complaints. Drowsiness develops long before there is sufficient retention of non-protein nitrogen to justify its consideration as a preuremic sign. Mental clouding may occur early, especially in alkalosis due to loss of hydrochloric acid. There may be irritability, introspective moodiness, general fretfulness and fault finding and other changes in temperament. None of these, however, is specific for alkalosis, and all are of too frequent occurrence among persons with gastrointestinal and other diseases to be of any great significance. A toxic delirium or other acute psychotic state occasionally appears. As dehydration and renal insufficiency increase, stupor and finally deep coma supervene. Once coma has appeared, death generally results. Tetany is very rare, as are other convulsive seizures, but muscular twitchings and hyperirritability of reflexes are seen in the late stages.

Renal Symptoms.—The changes in the reaction, composition and volume of the urine in alkalosis have already been described in the section on pathologic physiology. The importance of accurate estimation of the renal function prior to and during alkali therapy or gastric drainage cannot be over-emphasized. It is dangerous to rely on the reaction of the urine as a measure of alkalosis, because the urine may become neutral or acid as the alkalosis increases. Oliguria is a serious sign and demands immediate and vigorous treatment. In persons with known renal or urologic disease the use of alkalis should be undertaken with considerable caution and only after a complete assessment of the functional status. Urolithiasis of the calcium or magnesium type is a contraindication to alkaline therapy.

The renal insufficiency observed in alkalosis does not ordinarily produce subjective symptoms until advanced extrarenal uremia develops. Even then it is practically impossible to attribute this or that symptom to renal impairment as such. Uremic pericarditis does not seem to occur. There is no significant effect on the blood pressure. Hypertension in the presence of good renal function is not a contraindication to alkali therapy for peptic ulcer.

Blood Chemical Signs.—Chemical alkalosis exists whenever the serum carbon dioxide content exceeds 30 milliequivalents per liter (67 volumes per cent) and the pH is higher than 7.45. Clinical symptoms, however, are usually absent when the serum bicarbonate is less than 35 milliequivalents per liter (78 volumes per cent) and the pH below 7.5 to 7.55. Mild symptoms usually appear in the presence of 35 to 36 milliequivalents of carbon dioxide and a pH of 7.5 to 7.55. However, some patients may not exhibit any symptoms with a carbon dioxide content of 38 milliequivalents per liter (85 volumes per cent) and a pH of 7.55 to 7.57. When the bicarbonate concentration reaches 40 milliequivalents per liter (90 volumes per cent) or more and the pH is 7.6 or higher, symptoms are almost always present and are likely to be severe.

The serum chloride, as stated previously, decreases reciprocally with the increase in carbon dioxide. Thus, as the latter rises from 25 to 35 milliequivalents per liter (56 to 78 volumes per cent), the chloride concentration will usually fall from 105 to 95 milliequivalents per liter (372 to 337 mg. per hundred cubic centimeters). With further increases in bicarbonate, the chloride falls progressively and even in the absence of vomiting often drops to 75 or 80 milliequivalents per liter (266 or 284 mg. per hundred cubic centimeters). In patients with obstructive vomiting or gastric drainage as the cause of alkalosis, the serum chloride may fall to values of 60 milliequivalents per liter (213 mg. per hundred cubic centimeters) or lower. It is in such patients that dehydration and decrease in serum sodium or total base, as well as azotemia, develop.

A decrease in the normal sum of the concentrations of bicarbonate and chloride—125 to 135 milliequivalents per liter—should lead to the suspicion of a deficit in serum sodium or total base. This usually occurs after considerable vomiting and is associated with a lesser rise in serum bicarbonate than one would expect from the fall in chloride. The resultant lessened alkalosis is, however, accompanied by serious dehydration and sodium or total base deficit. This combination is likely to be worse for the patient than ordinary severe alkalosis. The accumulation of ketone acids in the blood as the result of starvation is relatively rare now that dextrose is given parenterally without much delay. Hence, it can readily be excluded as a factor in low serum base.

The retention of nonprotein nitrogen lags behind the serum electrolyte changes and depends considerably on the fluid intake and the urine volume, in addition to the degree of impairment of renal function. Therefore, it occurs more rapidly in patients with alkalosis due to vomiting or loss of gastric juice than in those on the regular alkaline management for peptic ulcer. Ordinarily, when moderate clinical alkalosis is established, the blood urea nitrogen will have risen from the normal 10 to 15 mg. per hundred cubic centimeters to about 25 to 40 mg. The nonprotein nitrogen will correspondingly increase to a level of about 50 to 70 mg. per hundred cubic centimeters. Further rises occur with increasing alkalosis and dehydration, but the values observed nowadays are much lower than those given in the earlier literature, for the reason that treatment is instituted sooner. The changes shown by the urea clearance test and other tests of renal function have already been mentioned in the section on the pathologic physiology of alkalosis. The presence of organic renal disease and of functional impairment prior to the onset of alkalosis lead to more rapid nitrogen retention and to higher levels. In advanced renal insufficiency, inorganic phosphate and sulfate retention occurs. Severe hemorrhage into the gastrointestinal tract will temporarily increase the nonprotein nitrogen level of the blood.

TREATMENT

The prevention of alkalosis should be easy even for those who think it necessary to treat peptic ulcer by means of alkalis. The addition of 5 Gm. sodium chloride to the diet is sufficient in most cases to prevent hypochloremia (Kirsner, *et al.*). Recent advances in the medical management of peptic ulcer should eliminate alkalosis entirely (see Chapter IX). It is obvious that the only safe way to administer alkalis is with the aid of repeated determinations of the serum carbon dioxide, chloride, *p*H and nonprotein nitrogen. The control values should be known before treatment is initiated. Large fluid intake and urine output are essential.

The treatment of clinical alkalosis consists essentially in reversing the procedures that led to its development. Therefore, in alkalosis due to the excessive administration of alkalis, the first step in treatment is to stop giving alkalis. Then, since a reduced salt intake and a fall in serum and urinary chlorides are constant factors in alkalosis, it is important to increase the sodium chloride intake, in order to promote diuresis and excretion of the excess bicarbonate and restore the serum electrolyte pattern to normal. At least 20 Gm. of sodium chloride should be given daily. This is best administered parenterally, because of the nausea and vomiting usually present. It should be given in the physiologic solution intravenously, in order to supply water at the same time. In patients who have recently suffered from hemorrhage from the gastrointestinal tract, it is safer to use the subcutaneous route. As soon as fluids can be taken orally, 3 or 4 liters should be given daily, or enough to produce a urine volume of 1,500 to 2,500 cubic centimeters.

For patients with gastric drainage or obstructive vomiting, an accurate daily record should be kept of the amount of gastric contents aspirated, vomited or drained. If the total exceeds 500 cubic centimeters daily, dangerous alkalosis and dehydration may result unless the intake of saline fluids, by whatever route, is sufficient to maintain a daily urinary output of 1,500 to 2,500 cubic centimeters. In any event, repeated analysis of the serum for carbon dioxide, chlorides, *p*H and nonprotein nitrogen is essential for good treatment. If alkalosis develops, enough physiologic solution of sodium chloride must be given parenterally to prevent dehydration and to produce an adequate urine flow. Dextrose solutions furnish calories, and water for urine formation, but cannot in themselves correct extracellular base or chloride deficits. The results of surgical treatment for the underlying lesion will be much better if the patient is properly prepared for it by being placed in normal water and electrolyte balance with little or no retention of nonprotein nitrogen.

For all alkalotic patients who are unable to eat, the parenteral administration of dextrose and aminoacids in amounts sufficient to prevent starvation acidosis and wastage of body protein is indicated. However, the diuresis resulting from dextrose solutions may cause further loss of badly needed chloride. Hence, one should not be satisfied with an increase in urine volume alone, but should make certain that an adequate chloride intake is being provided.

Acid-forming salts have been recommended in the treatment of alkalosis. They are irritating to the gastrointestinal tract, cannot be given intravenously or subcutaneously and are probably dangerous in advanced alkalosis. In general it is unnecessary to prescribe them. All that they can accomplish can be achieved as quickly and more safely with sodium chloride and water.

For patients with dehydration, oliguria and other signs of decreased circulating blood volume, plasma transfusions are of considerable value in improving the general condition and the renal function. Whole blood is preferable after severe gastrointestinal hemorrhage, even though the hemoglobin concentration may not be very low. One should allow for concentration of the blood due to dehydration.

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CHAPTER XII

CANCER OF THE STOMACH

INTRODUCTION

Cancer of the stomach is a medical problem both formidable and alluring. The proportion of cancer of the stomach in the total incidence of cancer is high. Cancer, according to Cramer, affects about 12 per cent of the population of most countries, and in this 12 per cent, cancer of the stomach is responsible for from 22 to 63 per cent of cancer deaths. There is wide variation in reported incidence of this type of cancer, but even the lowest figure, 22 per cent of all cancer deaths, is grim indeed, and stimulates increasingly all efforts to solve the problem of pathogenesis and, until this results in intelligent prophylaxis, to detect the early lesion and remove it. The sex incidence shows a preponderance of males (male deaths 23 to 45 per cent; female deaths 17 to 30 per cent), but Hurst pointed out that this variation may be due to the fact that in a number of women sufficient to make up this difference cancer of the breast or uterus causes death at an earlier age than that usual for cancer of the stomach. He also pointed out, however, that the usual incidence of cancer of the stomach was found in women who had survived uterine or breast cancer. The incidence of cancer of the stomach increases with maturity and is highest between the ages of fifty and sixty-nine. The proportion of persons with this type of cancer to the number of persons living also is highest in that decade. However, I found 5 per cent of 251 patients between thirty-one and thirty-eight years old, and 19 per cent in their forties. Before twenty-five the disease is undoubtedly rare. The youngest patient seen in the Lahey Clinic was twenty years of age.

PATHOGENESIS

The theories as to the development of cancer of the stomach are fundamentally those for cancer in any organ. Hurst, regarding the individual's predisposition to cancer as a first essential, added two other factors, an organic inferiority and chronic irritation. Cramer explained the occurrence of cancer of the stomach chiefly in middle and old age as due to the fact that all three factors, predisposition and the exciting organic inferiority and chronic irritation, have by then had time to become effective.

The two conditions commonly indicted as precancerous states in the stomach are chronic ulcer and chronic gastritis. The question of the relation of chronic ulcer to cancer has stimulated considerable investigation, from two angles: (1) how often has cancer been known to be secondary to ulcer—that is, to have arisen in the known ulcer; (2) how often is cancer found by the pathologist in the margin of a chronic ulcer. Clinicians differ in three respects by believing: (1) that no benign ulcer ever becomes malignant, and that the carcinoma is a distinct entity even when it is found at the site of a preëxisting ulcer; (2) that all benign gastric ulcers should be removed surgically because they all ultimately become malignant; (3) that certain unhealed ulcers become malignant, especially with recrudescence, while other benign ulcers heal, some never to recur, and others retain their benign character even with recurrence. Most clinicians, among them myself, concur in this last belief. In the pathologic studies of Stewart and of Orator, two facts related to this problem are outstanding: (1) that only 3 per cent of ulcers at the lesser curvature, but 33 per cent of prepyloric ulcers, show malignant transformation, this being indicated by observation of benign lesions with malignant changes; (2) the longer the history in proved cancer of the stomach (the long history suggesting ulcer-to-cancer transformation), the greater the incidence of free hydrochloric acid; whereas the shorter the history, the more likely is achlorhydria. In certain cases tests made prior to the development of carcinoma showed normal acid values and later development of carcinoma was attended by achlorhydria. In 2 of my cases, a gastric ulcer of the posterior wall with normal acid was observed to heal, and a recurrent lesion in the same area was found several years later with malignant changes and no acid.

The relation of chronic gastritis to cancer of the stomach has been studied from the pathologic aspect by many observers. The gastroscope will undoubtedly help to clarify the problem of gastritis in itself and in its relation to cancer. The chief effect of gastritis on the gastric mucosa is in the secretory glands, producing either achlorhydria or hypochlorhydria. Hurst expressed the belief, in which I concur, that individuals have a constitutional type of secretion, and that the effect of chronic irritation and gastritis on the secretory function of mucosal glands tends toward the achlorhydric or the hyperchlorhydric side, depending on this constitutional tendency. Hurst followed this hypothesis to the thought that a chronic ulcer is a possible result of chronic irritation and gastritis in the constitutionally hyperchlorhydric patient, while achlorhydria results from gastritis in the hypochlorhydric person. Complete achylia and atrophic gastritis represent the extreme results in the latter type. Konjetzny showed gastritis atrophicans hyperplastica to be constantly present with carcinoma, and it is believed by many that cancer develops by degeneration of the chronically inflamed gastric mucosa. Gastroscopic findings as they accumulate will probably support this theory, as does the not infrequent microscopic detection of malignant areas in the hypertrophic polypoid or the atrophic mucosa. Gutmann and his co-workers recognized a precancerous gastritis, but stated that they did not believe that classic chronic gastritis is a precancerous lesion.

Chronic gastritis affects the entire gastric mucosa, and cancer occurs commonly in the pyloric region. Hurst explained this apparent discrepancy in this theory by emphasizing the factor of chronic irritation resulting from friction, due to the churning type of peristalsis in this area of the stomach, as contrasted to the absence of the churning motion in the fundus and duodenal bulb.

The practical points in the relation of chronic gastritis to cancer are (1) the importance of avoiding and healing this condition to prevent a possible malignant transformation, and (2) the solution of the question whether an area of unhealed chronic gastritis should be removed surgically to prevent or remove early carcinoma. The latter question is, in my opinion, as difficult as it is in the case of gastric ulcer.

DIAGNOSIS

The early diagnosis of cancer of the stomach is often as strikingly difficult as the late diagnosis is easy. The clinical symptoms of loss of appetite, loss of strength and weight and pallor over a period of months or weeks and the finding of achlorhydria suggest at once well developed cancer of the stomach, and only when a normal radiographic contour of the stomach has been found is it necessary to consider cancer elsewhere or primary anemia. A palpable mass is frequently found (22 per cent in my series), and stools examined under controlled conditions show persistent occult blood. Radiographic examination shows the characteristic irregularity of the gastric contour, either in the fundus, where rigidity and narrowing are usually found as well, or in the media or antrum, where a constricting defect is often seen. With such a picture, the evidence is complete and the diagnosis certain, except for the remote possibility of gastric syphilis, usually eliminated by negative serologic results. Thus easily is late cancer of the stomach diagnosed.

The insidious onset of cancer of the stomach makes early diagnosis a challenge to the efficiency of public health education and to scientific acumen and accuracy and difficult even when both these factors operate successfully. The patient must be aware of the necessity of careful, oft-repeated investigation of any digestive symptom, and the physician must be equipped and trained to carry out such investigation and prepared to explain negative results without apology for the time and expense of the study. Only by such mutual understanding between the medical profession and the laity can the ideal of early diagnosis of this insidious disease be attained.

One of the most important points to be stressed, especially in health education, is the diversity in character of early symptoms. In a recent study, I found two stages in the histories of patients with gastric carcinoma. The first preceded the other by weeks or months, and the second was either a change in the character of the primary symptoms, *e. g.*, an intensification or change in time of occurrence of distress, or a completely new type of symptom. Such a combination might be distress followed in a few weeks by nausea and vomiting or loss of appetite followed by constipation. The textbook syndrome of loss of appetite, weight and strength was found worthy of its historic reputation as an indication of the disease when well developed, but abdominal distress, not always typically epigastric, is so important that all persons after a few days of abdominal distress should submit to a careful gastrointestinal study. If, after showing negative results, the patient continues to have persistent symptoms, and if, within a month, the study is repeated, I believe that earlier lesions of the stomach will undoubtedly be discovered. The distress is usually epigastric, but is occasionally general abdominal or localized in the right or left upper quadrant or the shoulders. It is often relieved by ulcer treatment and may even have short periods of remission characteristic of ulcer. Loss of weight varies from under 10 to over 70 pounds. Loss of appetite is usually progressive, and to be of any value as a warning it should be seriously considered when first noted. Often patients and physicians are content to explain symptoms of failing strength, weight and appetite on the basis of nervous fatigue. This error is particularly likely if the patient is known by the physician to be under great strain or to have a history of neurosis. Every clinician should supplement a careful physical examination with a careful gastrointestinal study when any patient over thirty considers it necessary to consult a physician for fatigue or debility, even though circumstances appear to explain his condition.

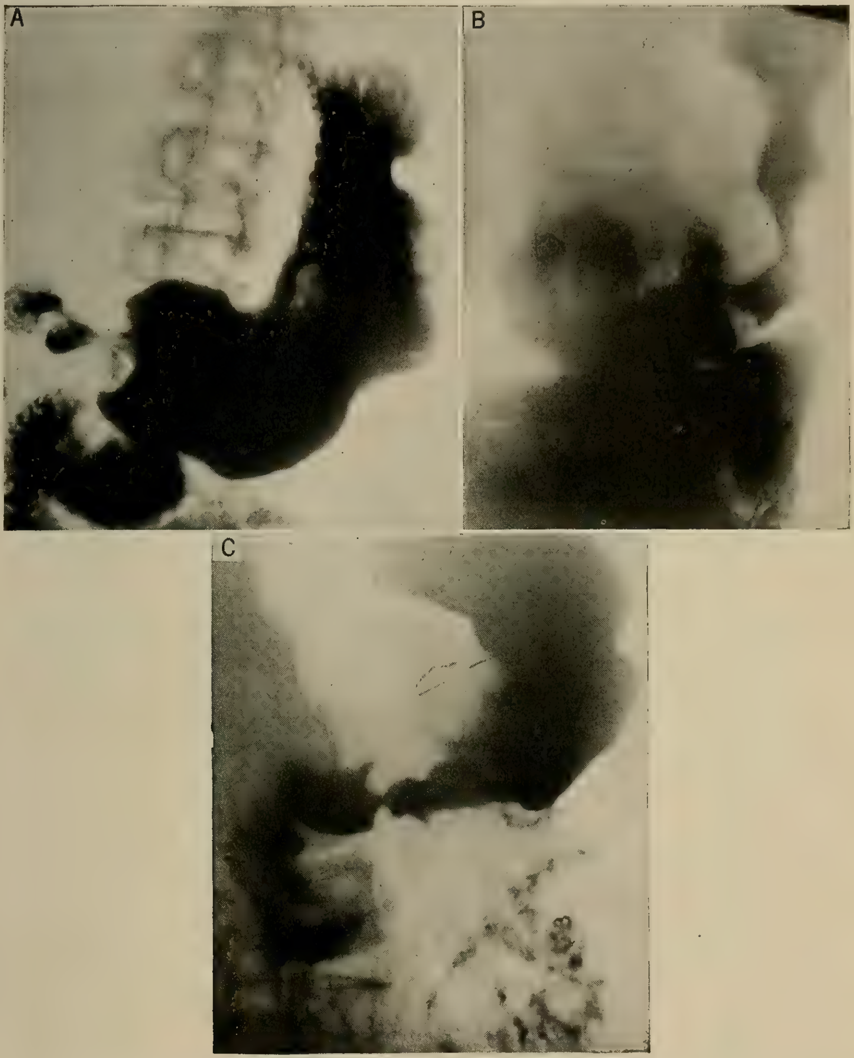

Fig. 58.—Roentgenograms showing large infiltrative lesions of the cardia, media and antrum with metastases. They were inoperable at the first examination.

Physical Examination of the patient with late cancer of the stomach reveals four telltale findings: pallor, evidence of loss of weight, an abdominal mass and evidence of metastases either in the supraclavicular lymph nodes or in the rectal shelf. The abdominal mass is usually in the epigastrium but may be in the left upper quadrant, rarely in the right upper quadrant or occasionally in the lower part of the abdomen, according to the location of the tumor in the stomach and of the stomach in the abdominal cavity. It is always movable and frequently tender. If the lesion has produced obstruction, there may be visible peristalsis, and not infrequently the outline of the mass itself is visible. Metastases are of course palpable when in the supraclavicular lymph nodes (the so-called Virchow or sentinel node) or in the rectal shelf; but they may be also in parts of the body not readily accessible to palpation, such as the peritoneum and omentum, the liver, the lungs and the bones, and may be symptomless. With very early cancer of the stomach the physical examination is usually as noncontributory as with cancer. There may occasionally be epigastric tenderness, but no other evidence of the beginning lesion.

Adequate study of a patient presenting any evidence in his history or physical examination at all suggestive of cancer of the stomach includes (1) examination of the gastric contents after a test meal to determine the presence or absence of free hydrochloric acid; (2) blood counts, hemoglobin determination and smear; (3) examination of stools for occult blood under controlled conditions; (4) careful radiographic examination both fluoroscopically and with films, and (5) gastroscopy. It is assumed that the physical examination includes rectal examination and proctoscopy.

Chemical Examinations.—The gastric contents after a test meal show achlorhydria in 60 per cent of cases of cancer of the stomach. The incidence of achlorhydria in the general population is probably less than 15 per cent. In many cases of cancer there is hypochlorhydria, which in the later stages becomes achlorhydria. The importance, therefore, of the acid findings cannot be gainsaid. However, normal or even high free hydrochloric acid does not insure benignity. Therefore, while the absence of acid increases the suspicion of cancer, its presence must make the diagnostician no less vigilant. Particularly should a change from a normal to a low acid value or to achlorhydria in a patient with an ulcer history, or even without previous gastric disease, be regarded with some suspicion. Furthermore, patients with known achlorhydria, particularly those with a history of a healed gastric ulcer, should have periodic check-up *x*-ray examinations so that the beginning of carcinoma may be detected.

Secondary anemia is of considerable significance, but it is rarely found until the lesion is well developed. Occult blood in the stools, however, under controlled conditions, is important evidence of an ulcerating lesion, and in the presence of other evidence is confirmatory for cancer.*

X-ray Examination is the most important aid in diagnosis at the physician's disposal today. It has two purposes, the detection of the lesion and the determination of its location and operability. Visualization of the stomach is best obtained for both fluroscopic and film examination by first outlining the rugae of the stomach by administration of a small amount of a thick, smooth mixture of an opaque substance, such as barium sulfate, and by observing their conformation both with and without compression. In this way abnormal mucosal patterns and hypertrophy or atrophy of the mucosa can be noted. Sometimes the patient must be placed in standing, prone and supine positions before differentiation between normal and abnormal patterns can be definite. In the normal stomach, six to eight roughly parallel folds of mucosa (rugae) are seen throughout the length of the stomach; these maintain their contour even with pressure under the fluoroscope. An irregularity in this pattern around an area devoid of rugar markings is evidence of an organic lesion. Evidence for benignity is found in a regular radiation of this marking around a central point which is the crater of an ulcer, whereas grossly irregular markings around the central point or an absence of markings over a poorly defined area are evidence for malignancy. This method of visualization with a small

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* The persistance of occult blood in the stool after two or more weeks of ulcer management is significant of a gastric carcinoma—with supporting roentgen evidence of a gastric lesion.—EDITOR.

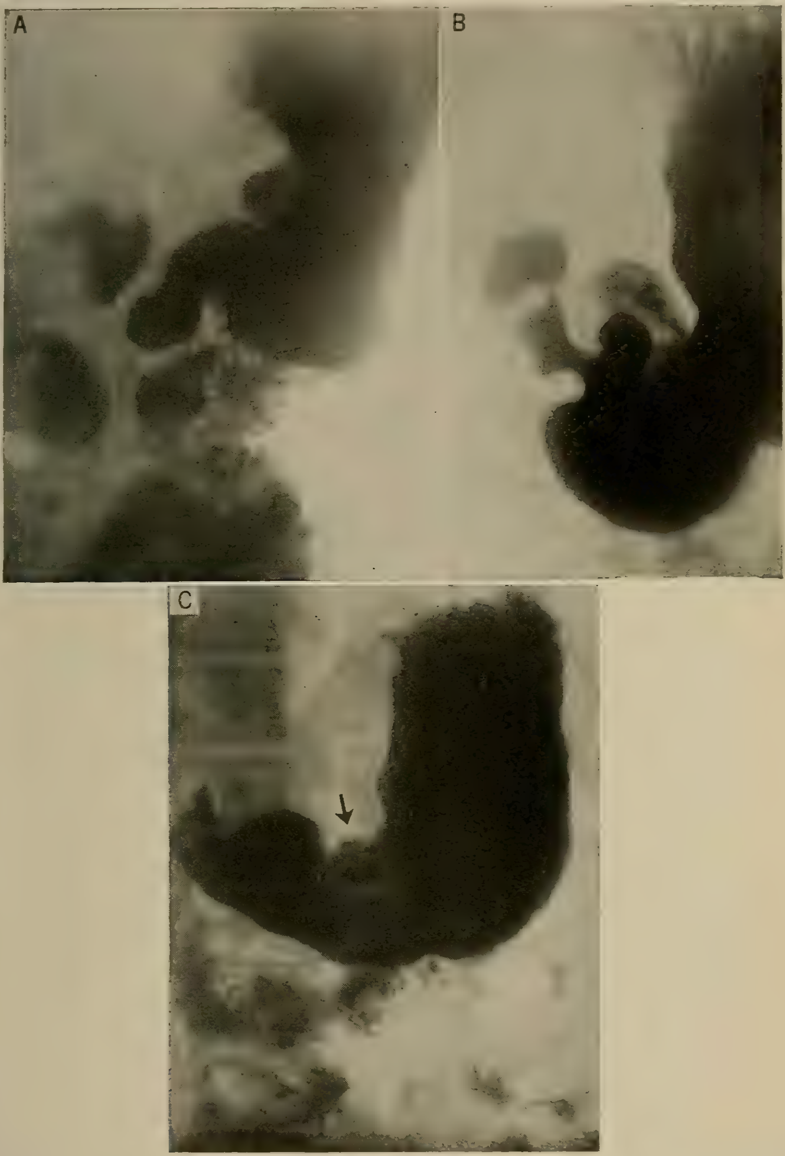

Fig. 59.—Roentgenograms showing, *A* and *B*, malignant ulcers with the typical meniscus around the base of the crater; *C*, unusual picture of benign ulcer with meniscus.

amount of barium and with deep palpation is especially useful in revealing lesions of the anterior or the posterior wall of the stomach, which do not involve either curvature and which, therefore, in their early stages fail to produce any deformity of the gastric contour. Then the opaque material is given in sufficient quantity to fill the stomach, and the resulting contour, tone and motility of the stomach are carefully noted.

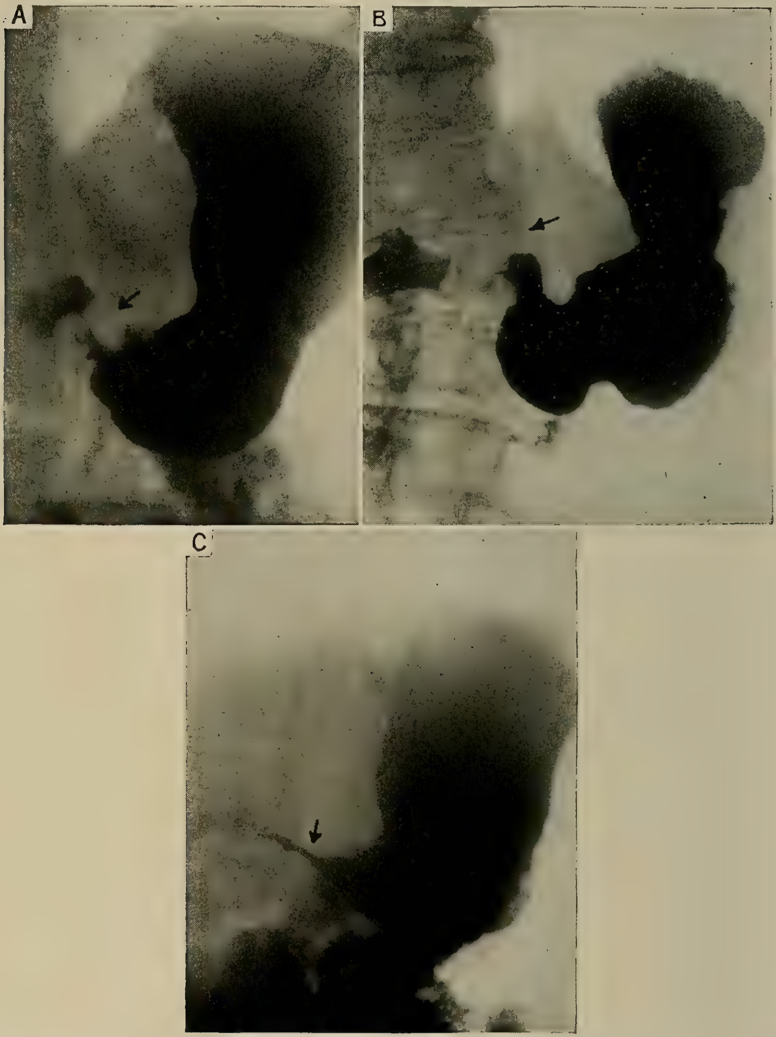

Fig. 60.—Roentgenograms showing, *A*, spasm of the prepyloric antrum with no organic lesion; *B*, early malignant lesion of the prepyloric antrum; *C*, late malignant lesion of the prepyloric antrum.

The commonest *x*-ray findings in late cancer of the stomach are (1) a rigid, contracted appearance in any part of the stomach wall through which no waves of peristalsis pass, indicating a submucosal involvement of the wall; (2) an irregular, moth-eaten appearance with a failure of the involved area to contract normally, indicating a well developed ulcerating lesion; (3) a narrowed, obstructed area in any part of the stomach, with loss of flexibility in the stomach wall adjacent to this area. Such findings are, except for the few cases of gastric syphilis, pathognomonic of cancer, and the only remaining question concerns operability.

For *x*-ray diagnosis of the early lesion two major problems are involved: (1) differentiation of an organic lesion from a functional condition simulating an organic lesion; (2) differentiation of a benign ulcer from carcinoma or from ulcer with beginning malignant changes.

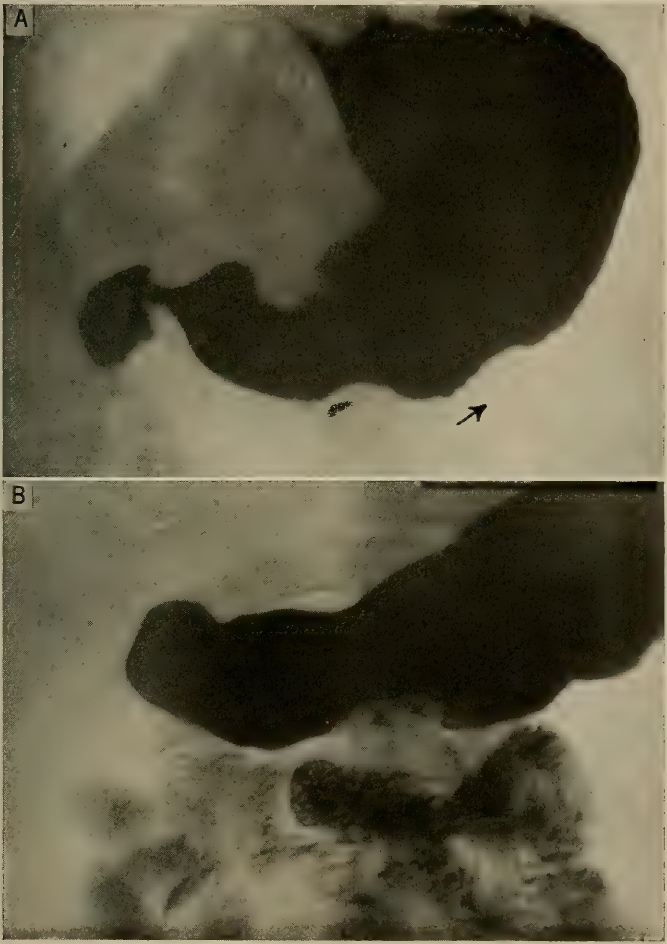

FIG. 61.—Roentgenograms showing, *A*, carcinoma of the greater curvature; *B*, hypertrophic gastritis of the greater curvature.

The commonest phantom lesions simulating carcinoma are those caused by spasm, particularly in the pyloric region of the stomach, where spasm may produce a rigid contracted appearance, often indistinguishable from that produced by carcinoma. This makes it necessary (1) to differentiate spasm and organic disease; (2) to find the gastric or extragastric cause of the spasm, and (3) to identify the organic disease, if it exists. Spasm may persist in spite of the administration of medicinal antispasmodics, and sometimes in spite of these in addition to rest, the natural antispasmodic, making visualization of the mucosal pattern of the pylorus impossible. The defect may be ascribed erroneously to spasm and no operation for cancer done, or a useless operation may be performed for spasm. Other errors are due to adhesions or a scar from a healed ulcer or a loop of jejunum in close proximity to the stomach, either of which may simulate early cancer or conceal a malignant lesion.

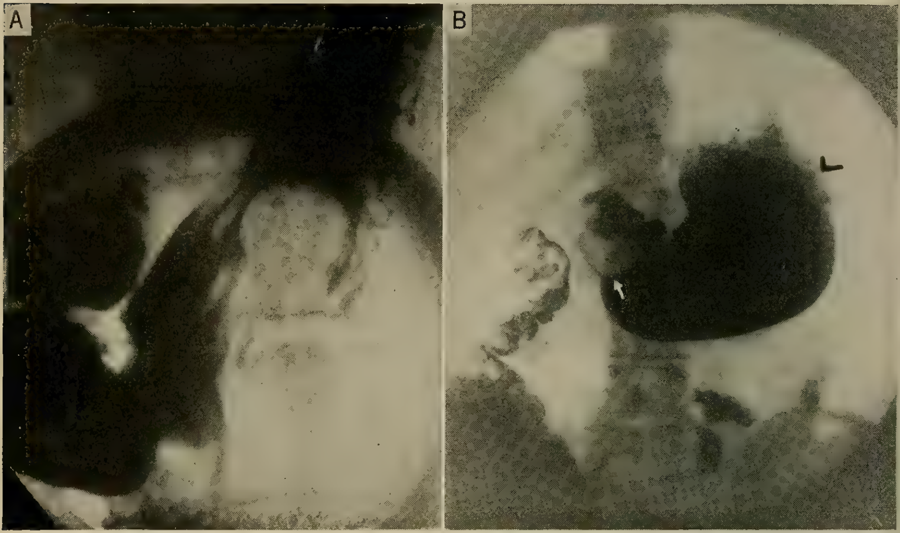

Fig. 62.—Roentgenograms showing, *A*, benign tumor; *B*, carcinoma with roentgen appearance of a benign tumor.

Differentiation of a benign ulcer from a malignant lesion must be made wherever the lesion is located. Greater curvature lesions are almost always obviously malignant, although occasionally a mucosal irregularity due to hypertrophic gastritis has the appearance of a malignant lesion. Since cancer does occur in ulcer form and certain cancers arise from ulcers, all apparent ulcers on the gastric side of the pylorus must be suspected of harboring possible malignant changes or of being malignant instead of benign, and any lesion which has the typical appearance of an ulcer—a crater or niche defect, usually of smooth contour with flexibility of the adjacent stomach wall—must be seen to disappear under treatment. When the diagnosis is doubtful, the patient should be placed on careful treatment under observation and three criteria used to determine complete healing: (1) disappearance of the defect under *x*-ray, (2) disappearance of occult blood in the stools and (3) disappearance of symptoms. These criteria are usually fulfilled within three to five weeks. There may occasionally be some delay in the first, but progress in this direction must be noted within a few days and must continue, even if slowly, to the point of complete disappearance. Even large craters can be seen to vanish within a few weeks. This policy of trial management in diagnosis is desirable for two reasons: (1) it presents exploratory operation with the diagnosis still remaining questionable, even when the lesion is actually seen and palpated by the surgeon; (2) it leaves no doubt as to the procedure to be used at operation, for if the lesion has not fulfilled the criteria noted, there is reasonable suspicion of cancer, and the lesion should be removed. Patients with healed gastric ulcers should be reëxamined at regular intervals, particularly if there is the slightest recurrence of symptoms, in order to avoid missing the early beginnings of recurrence with malignant changes.

The location of the lesion has long been considered to be of great significance in differentiation. Both malignant and benign lesions occur in all parts of the stomach, except on the greater curvature, where the rare ulcerating lesion is always malignant. It has been suggested that in the prepyloric area malignancy is inevitable when an ulcer remains unhealed, and this area is the site of most carcinomas which develop without an ulcer background. Furthermore, it is difficult to follow the progress of healing in an ulcer in this region. For these reasons, this area is often the site of puzzling diagnostic problems. While autopsy reports indicate that ulcers occur and do heal in this area with considerable frequency, yet because it is danger zone for cancer, subtotal gastrectomy rather than further medical management is desirable if there is the slightest doubt as to the flexible integrity of the stomach wall in this region. In the cardia, benign ulcers are rare, and most malignant lesions have a rigid, irregular appearance which leaves no doubt as to their nature. The conformation of the rugae is also irregular when the lesion is malignant. However, because the lesions usually require total gastrectomy for removal, with a less promising outlook for the postoperative comfort and well-being of the subject, the discovery of the early lesion is possibly less vital here than in a location accessible to other surgical measures.

Gastroscopy.—The detection of early carcinoma of the stomach will undoubtedly be aided to a great degree by increasing experience with the gastroscope. The typical appearance of the ulcerating carcinoma is of an eroded area of ill-defined edges, with an irregular distortion of the mucosal pattern for some distance around it. This is in contradistinction to the clear-cut, sharp-edged appearance of the benign ulcer, around which the mucosal pattern is usually regularly radiating toward the lesion. The base of a malignant ulcer may be red and granular, with raised bleeding or gelatinous vesicles showing through. The base of a benign ulcer is usually covered with a grayish exudate, and the eroded mucosa is rarely seen. The infiltrating lesion of the wall is detected through the gastroscope by its atrophic mucosa, grayish color and lack of flexibility to peristalsis. Lesions which protrude into the lumen are easily detected if they occur in areas visualized with the gastroscope. The areas most difficult to visualize with the gastroscope are the posterior wall of the stomach and the cardia. The smooth discrete tumor should always be suspected of malignancy, for it is impossible to distinguish the benign leiomyoma from the leiomyosarcoma except by histologic examination. The pedunculated smooth tumor thus visualized may be a benign adenoma or an adenocarcinoma, with extension of malignancy through the pedicle into the gastric wall. Detection of all such lesions with the gastroscope should therefore be followed by their removal if early malignant lesions are to be found. The typical raised submucosal adenocarcinoma is of irregular circumference, and is irregularly nodular, with the familiar appearance of this kind of cancer.

Differential Diagnosis.—Carcinoma of the stomach must be differentiated from the following conditions: (1) a functional or inflammatory disturbance resulting in spasm which distorts the contour of the stomach; (2) a benign ulcer; (3) a benign tumor—notably leiomyoma or polyp; (4) syphilis. The differentiation from ulcer and functional or inflammatory conditions has been discussed.

Since polyps so often become malignant and leiomyomas cannot be differentiated grossly from leiomyosarcomas, it is my belief that no attempt related to operability should be made to differentiate benign lesions of this group from malignant ones, and the diagnosis should be made only by histologic examination after their removal. In the case of multiple polyps or so-called polypsis of the stomach with no clinical evidence of malignant change, the degree of involvement of the stomach and the intensity of symptoms, notably hemorrhage, are the criteria on which treatment depends. If the lesions are so extensive that an almost total or total gastrectomy must be done to remove them, and no serious symptoms are present, it is usually better judgment to risk malignant transformation than to remove most of or the entire stomach. For a single polyp or localized limited area of polyposis accessible to operation, resection with removal is desirable, since in general the change of the polyp from benignity to malignancy is frequent.

Differentiation from gastric syphilis is sometimes difficult. Syphilis of the stomach is exceedingly rare. The radiologic and gastroscopic appearance closely simulates that of carcinoma. It occurs usually in the media of the stomach and is usually symptomless. Positive serologic results are of aid when the diagnosis is doubtful; and when the lesion is strongly suspicious, an intensive course of antisyphilitic therapy resulting in x-ray disappearance of the defect establishes the diagnosis of syphilis.

Complications.—The complications of gastric cancer are (1) perforation of the lesion into adjacent organs, with extension, and adhesions from inflammatory reaction around the lesion; (2) hemorrhage; (3) obstruction, and (4) metastatic involvement of other parts of the body. Acute perforation is rare. Rarely a complete perforated lesion requiring immediate suture has been followed by recurrence. Chronic perforation, especially into the pancreas, more rarely into the duodenum or jejunum, is often found late in the course. Since this is a gradual process and since it is walled off by its gradual development, it is recognized clinically only by the onset of severe pain, particularly when the pancreas is involved, and radiologically by the fixation of the involved stomach wall. In the presence of late lesions with this complication, a palpable mass is usually found, usually owing to the lesion and the adhesions around it. Occasionally, in late involvement fistulous tracts are found extending from the original lesion into other organs. Massive hemorrhage occurs in carcinoma of the stomach much less frequently than in benign ulcer. Oozing and minor hemorrhages are frequent and are evidenced by the presence of occult blood in the stools and by the brown color of gastric contents. Obstruction occurs when the lesion surrounds either orifice of the stomach or constricts the media to an hour-glass shape. This complication is most frequent at the pylorus when the lesion is prepyloric. It is evidenced clinically by pain, nausea and vomiting and radiologically by a rigid constricted area at the pylorus and by abnormal barium retention in the stomach. An obstructing lesion at the cardia produces difficulty in swallowing, and the esophagus and cardia of the stomach may be involved to an equal degree.

Hour-glass constrictions of the media are rarely extensive enough to obstruct completely before death occurs from metastases or the lesion is removed surgically.

Metastatic involvement occurs in the omentum and peritoneum, liver, left supraclavicular lymph nodes, rectum, ovaries, lungs, bones, adrenal glands and brain, the incidence being approximately in that order. A careful rectal examination should always be done to determine the presence of the so-called rectal shelf, a metastatic involvement of the peritoneum palpable through the rectum. Enlargement of the left supraclavicular lymph node (Virchow or sentinel node) is easily palpable, and in advanced disease omental, peritoneal and hepatic metastases may be palpated. When the liver is extensively involved, ascites follows. An *x*-ray examination of the lungs and bones should always be made before operation, as even a small, readily removable gastric lesion may have metastases in such distant parts and thereby be rendered clinically inoperable.

PATHOLOGY

Carcinoma of the stomach may be found in any part of the stomach, on either lesser or greater curvature and on either wall. Three types occur: (1) a raised tumor proliferating to a variable degree into the gastric lumen; (2) a thickened, indurated, more or less irregularly diffuse infiltration of the wall; (3) an ulcer-like crater.

The first type is ordinarily produced by the adenocarcinoma—usually a proliferation of the gastric crypts with penetration of the submucosa and muscularis. Necrosis, ulceration and infiltration of the adjacent omentum and viscera follow with extension. Obstruction often occurs early, especially if the growth is in the antrum or at the pylorus. Much less frequent is papillary adenocarcinoma, arising from a polyp or pedunculated adenoma and invading the wall of the stomach through the stalk. With this, also, the blood supply is impaired, and necrosis and ulceration occur. Rarely obstruction occurs, usually the intermittent type resulting from the ball-valve action of a pedunculated mass into the pylorus. Another variation is the colloid carcinoma with a predominance of the mucoid-producing cell, with less protuberance into the gastric lumen and with invasion of the muscular coats by mucinous material. Development and metastasis are early.

The second type, the irregularly diffuse infiltration, is either the spheroidal cell carcinoma of rapidly developing malignancy or the scirrhous carcinoma. The former appears as a raised thickened area of mucosa, involves the crypts to only a slight degree and appears to have its origin in the chief cells of the gastric glands and to penetrate the mucosa, submucosa and muscularis. The cells are spheroidal and are arranged in columns or small nests. Metastasis to the regional lymph nodes is early. The diffuse scirrhous carcinoma is characterized by hyperplasia of fibrous tissue, with columns of irregularly shaped cancer cells between its strands. It spreads rapidly and may transform the entire organ into the so-called leather-bottle stomach, a thick-walled inflexible structure, the lumen of which may be contracted. The peritoneal surface of the stomach so involved shows white streaks formed by the tumor in subserous lymphatic vessels.

The third type, the ulcer-like crater, is of the same scirrhous type, but is circumscribed like a benign ulcer, round and deep or shallow and irregular. The base is formed by infiltrated muscularis or gastrohepatic omentum which the lesion has penetrated.

LIFE HISTORY OF CANCER OF THE STOMACH

The spark of life which engenders cancer is still nebulous. Hence, it is impossible to discuss intelligently the earliest beginning of cancer of the stomach. Assuming a predisposition, the next factor in its generation is the choice of organ. Since all organs fulfil their function constantly throughout life, each one fitted by nature to carry its burden of work and each one equally influenced by the relation of rest and labor to which the body is exposed, another condition, called by Hurst organic inferiority, must play its part as a secondary factor in focusing the predisposition of the individual toward one organ. However, as in 40 per cent of cases this organ is the stomach, there must be a third factor, chronic irritation. It can only be assumed, therefore, that in this gastric pouch—this digestive workshop and laboratory, where much chemical change and vigorous mechanical work are constantly being done—a few cells, naturally not the strongest of the body, which in turn is not adequately resistant, have been subjected too constantly to chemical or mechanical injury, and a transition takes place from normal cell growth and replacement to an abnormal process. Only by local removal of such an area of abnormal cell life can the normal cell life of the rest of the stomach be maintained, for the abnormal pattern will otherwise too soon supplant the normal.

PROPHYLAXIS AND TREATMENT

With the important links in the development of cancer, *i. e.*, the predisposition and organic inferiority, still obscure, it is perhaps useless to speculate on prophylaxis. Certainly neither genetics nor early care can yet guard the human being against the development of cancer of the stomach. However, whether the individual has embarked on life with or without a predisposition to cancer and with a stomach by nature strong or weak, he can and should regard the activities of his stomach with the interest of a guardian. The habits of eating and the choice of material are the immediate considerations. In these days of intense interest in dietetics, it is not at all difficult for the physician to stimulate his patient to a desire to know what and how so eat. The food faddists and cultists can be combated by adequate scientific control of dietetics and widespread instruction in the physiology of the digestive tract. Gourmandism and even the minor temptations of appetite should be recognized as irritating factors. The stomach itself helps most effectively by its signs of rebellion or coöperation. If the human being could be imbued with the will to eschew all pleasures of taste which result in stomach consciousness or stomach discomfort, he would undoubtedly avoid one obvious source of gastric irritation. It should be remembered that the discomfort which has to be assuaged with an alkali or a hot water bottle has been, in spite of its relief, a source of irritation to the stomach. The effects of excessive alcohol and smoking have now been recognized as a definite cause of gastritis, both acute and chronic. Since the control of gastric function depends on the nervous system, this, too, should be protected by the individual by adequate rest, exercise and philosophy. General and specific care to prevent or heal gastric ulcer and gastritis will unquestionably reduce the incidence of gastric carcinoma. However, study of the histories of patients with gastric carcinoma does not lend support to any theory as to the cause and prophylaxis of this type of cancer. Frequently these patients have been exceptionally well and vigorous and of normally good habits of living, so that no one factor can be indicted as a precipitating cause of this disease. However, histories are often defective in data which concern habits of living.

Ideal Therapy.—The ideal therapy of gastric cancer is complete removal of the early lesion. Good results even with the earliest lesion depend, however, largely on its location. If it is in the distal two-thirds of the stomach, successful resection restores the patient to normal health for a varying period, depending on metastatic involvement. Patients have been reported living and well fifteen years after resection. The gastric stump takes on the function of the complete stomach in all respects except the secretion of hydrochloric acid, and even in its appearance it may resemble a small complete stomach. With frequent small meals and the administration of hydrochloric acid, the nutrition and the comfort of the patient can be entirely maintained. Measures must usually be taken to prevent severe anemia of the macrocytic type. If, however, the lesion is at the cardiac end of the stomach and total resection must be done, the outlook for survival and for postoperative comfort is considerably diminished. The Bilroth I and the original Bilroth II operation have been discarded by many surgeons because the former does not allow wide enough resection and the latter has poorer functional results than the Polya type of resection, anterior and posterior, now in rather general use. The anterocolic modification (Balfour) of the Polya operation with treatment of the stomach stump is the method of choice in most clinics. The postoperative difficulties are associated with spasm of the esophagojejunal stoma and with dilatation or inadequate power of absorption of the small intestine. These conditions produce discomfort with swallowing and abdominal distress and diarrhea following the ingestion of food, but in some instances dilation of the esophagus and the administration of frequent small, easily digestible meals with hydrochloric acid bring about relative comfort and digestive power. The degree of metastatic involvement is not always a guide in the matter of operability, particularly when lymph nodes adjacent to the lesion are found. Histologic examination of many of these apparently involved lymph nodes shows an inflammatory process only, and even in the presence of carcinomatous nodes long postoperative survivals have been reported. This is true also when solitary or rare nodules are found in the liver. Palpable metastases to the rectal shelf, on the other hand, indicate extensive involvement, making gastric operation unwise. *X*-ray examination of the lungs and bones should always influence the decision for or against operation, as occasionally small lesions are found in the lungs and bones which are not visualized fluoroscopically, and in their presence operative procedures on the stomach are futile. Palliative operations, except in cases of complete obstruction, are usually of no value as far as survival is concerned, various reports indicating that the duration of life with or without palliative surgical measures in the presence of an unresectable involvement is about the same. The mortality of palliative operations, with no increase in expectancy of postoperative survival, makes this procedure useless except when there is need of immediate relief from obstruction in the patient who is otherwise in relatively good condition.

The end-results of surgical treatment are still far from encouraging.* They vary in the hands of different surgeons, probably owing to the individual estimation of operability. When resection is done in spite of small liver metastases the group of patients living comfortably for two or three years is larger than when a finding of any metastatic involvement, even to the local lymph nodes, is considered a contraindication for resection. On the other hand, where only the most conservative operations are done for the earliest lesions the proportion of patients living five years after resection is higher. A recent report by Livingston and Pack of 1,100 cases, covering operable and inoperable lesions, showed 1 instance in 20 of survival five years after operation. In a series studied by me, about one-seventh of patients who had resection lived four or more years after the operation. Scattered throughout the literature are isolated reports of patients living ten to twelve years after resection; some of these underwent resection in spite of lymph node involvement.

Medical Treatment.—Medical treatment consists in symptomatic and supportive treatment of inoperable lesions and postoperative management of operable ones. Patients usually restrict their diet to those foods which in their experience are most easily digested, and in many cases an ulcer diet is best tolerated. In the presence of the non-ulcerating type of carcinoma, hydrochloric acid usually adds to digestive comfort; whereas for the ulcerative type, although hypochlorhydria or achlorhydria is usually present, alkali therapy often gives temporary relief of discomfort. After resection, medical treatment should be directed toward the establishment of a nutritious, balanced and easily digested diet in frequent small meals, of a routine of adequate rest and exercise to maintain general body tonus and digestive function and of vigilance in preventing or treating the anemia which often follows. The administration of iron and vitamins is practically always indicated. Not infrequently the use of hydrochloric acid is of value in preventing too rapid evacuation of the gastric stump and uncomfortable dilatation of the jejunum.

Radiation therapy will probably have a greater role in the management of gastric carcinoma in the future than it has today. With the early discovery of a lesion and the immediate use of radiation, progress should be made in the fight against cancer of the stomach. The application of radiation to the involved area without destruction of intervening or adjacent normal tissue has been and still is the obstructing problem. The development of high voltage, deeply filtered x-ray therapy so that radiation may be applied deeply without injury to other tissue, or possibly its application under gastroscopic control, is the probable solution to this problem. As a palliative measure, especially in conjunction with palliative gastroenterostomy, it has been used successfully.

CONCLUSIONS

With the present knowledge of cancer in general and carcinoma in particular, the problems associated with this disease resolve themselves into (1) a continued search for clues to the fundamental cause; (2) in the absence of that knowledge, an increasing endeavor to detect the early lesion and remove it, and (3) an attempt to guard the patient against any possible causative factors even though their relation is not conclusively proved. Early diagnosis is often exceedingly difficult, for two reasons: (1) the symptoms are so indefinite or so late in appearing that investigation is not sufficiently early; (2) even with the most careful investigation, an early lesion may be mistaken for a benign ulcer or a functional condition. The vagueness and latency of the symptoms are due to the fact that gastric symptoms are usually caused by erosion or obstruction and many of these lesions either never erode the mucosa or do so very late and rarely obstruct in the earlier stages. The confusion of early carcinoma with benign ulcer or a functional condition makes it necessary to have no doubt of the complete healing of an ulcer and to differentiate functional conditions by follow-up observations or exploratory laparotomy. The attempt to guard the human being against carcinoma by consideration of causative factors must be made with still existing doubt as to their definite relation, but the integrity of the stomach wall should be preserved by complete healing or removal of gastric ulcers and by serious efforts to heal all forms of gastritis.

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* Patients who still persist in having free hydrochloric acid may offer a better prognosis. Further, if carcinoma develops in a patient with normal free acid and achlorhydria develops later, the prognosis, in my experience, should be "well guarded."—EDITOR.

Finally, it must be acknowledged that the results of treatment of cancer of the stomach are so discouraging that interest in its early detection might appear unavailing. In my opinion, however, every patient should be regarded individually and not only should be detached from the aura of dismal statistical evidence but should be envisaged as having the possibility of several years of comfortable living. With this possibility, the development of all measures to detect the very beginnings of the lesion, not to mention their prevention, may indeed be considered a stimulating subject for further intensive research and interest.

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CHAPTER XIII

BENIGN TUMORS

More than 1,500 cases of benign new growth of the stomach have been reported in the literature up to the present. In most of the reported cases the tumor was found at necropsy, and until recently the true nature of lesions found at operation has not been recognized beforehand. The experienced physician or surgeon always regards gastric tumors with suspicion, for the simple reason that the majority of them are actually malignant. Some of those which are actually benign sooner or later undergo malignant change; however, the possibility that a new growth may be benign is of practical diagnostic, prognostic and surgical significance.

INCIDENCE OF BENIGN TUMOR

Prior to 1913 the incidence of benign tumors at necropsy in various European hospitals ranged from 0.007 to 0.04 per cent. Tilger[36] and Eliason and Wright[7] found incidences of 0.4 and 0.62 per cent, respectively; yet as early as 1864, Ebstein[5] found an incidence of 2.3 per cent. As late as ten years ago, Stewart[34] found an incidence of 0.43 per cent in 11,000 necropsies. In 1930 Hillstrom[15] found that about 5 per cent of all tumors discovered at necropsy or removed at operation were benign according to the records of the department of pathology of the University of Minnesota. Six years later, Rigler and Ericksen[29] reported that approximately 25 per cent of a series of 194 tumors of the stomach or duodenum observed at necropsy were diagnosed as benign. Rieniets,[28] in 200 consecutive necropsies, made a meticulous search for tumors in the gastric wall and demonstrated small single or multiple gastric leiomyomas in 17 per cent of cases.

Nadeau and MacCarty[24] stated that 1.2 per cent of all gastric tumors were benign. In 1922, in collaboration with Senty, I[8] reported 27 cases, observed at the Mayo Clinic in approximately twenty years, of benign tumor of the stomach in which the diagnosis was verified at operation. In the same period, operation disclosed 2,168 malignant tumors of the stomach. The 27 benign tumors, therefore, comprised 1.23 per cent of all gastric tumors found at operation. A clinical diagnosis of carcinoma of the stomach was made in 2,285 additional cases in the same period. The 27 cases of benign tumor, therefore, comprised 0.6 per cent of the 4,480 cases in which a diagnosis of benign or malignant neoplasm of the stomach was made clinically or at operation. Others[6] reported a similar incidence. However, ten years later Lockwood,[20] in a small series of cases, observed that about 5 per cent of all gastric tumors found at necropsy or removed at operation were benign. On the basis of roentgen examination in a large number of cases, Kirklin and Weber[18] stated that less than 2 per cent of all gastric tumors coming under clinical observation were benign. But Rigler and Ericksen[29] made a diagnosis of benign tumor in 11 per cent of 239 cases of tumor of the stomach in which roentgen examination was performed. The number of cases of benign tumor of the stomach coming under clinical observation has been constantly increasing.[2] As evidence of this increase, 118 additional cases, making a total of 176 cases, have been observed at the clinic (Table 5).

Table. 5—Benign Tumors of the Stomach Observed at the Mayo Clinic

Type of tumor	Cases
Adenomatous polyp	80
Leiomyoma, fibromyoma, adenomyoma and myxofibroma	44
Adenoma	19
Polyposis	10
Hemangioma	6
Fibroma	6
Neurofibroma	5
Dermoid cyst	3
Papilloma	2
Lipoma	1
Total	176

Routine resort to roentgen examination and the marked improvement in technic and the more systemic search for these lesions at necropsy have been largely responsible for the increased incidence. The actual incidence, however, is undoubtedly even greater than one would expect from data based on clinical findings. Many of these lesions are asymptomatic and, therefore, do not come under observation. Others may be easily overlooked on roentgen examination. Moreover, carcinomatous lesions eventually seen at necropsy may originally have been ordinary adenomatous or papillomatous polyps. However, it must be remembered that many of these smaller tumors found by systemic search at necropsy have no real practical significance, and that even the larger ones, in contrast to gastric cancer or ulcer, are rarely the sole cause of a patient's seeking medical relief.

ETIOLOGY

Aside from the generally held views regarding the origin of neoplasms, other explanations with respect to benign tumors have been advanced from time to time, but have not found general acceptance. Ewing[9] expressed the opinion that an original structural anomaly or local tissue predisposition is present, but that mechanical and inflammatory factors have much influence on the progress of the growth. Stewart[34] maintained that a sessile plaque of glandular over-growth can be converted into a pedunculated polyp as the result of the muscular movements of the stomach, aided perhaps by the force of gravity. Faber,[10] Konjetzny[19] and a number of other observers maintained that chronic gastritis bears a close causal relation to benign gastric polyp and polyposis, although Stewart[34] was not ready to share this point of view.

PATHOLOGIC FEATURES

The tumors vary in size from that of a hemp seed to that of an adult head. They originate from the mucosa or submucosa, being either broad based (sessile) or pedunculated. Exceptionally they are large, but the average diameter is 2 or 3 centimeters. A few tumors project outside the stomach, and are usually pedunculated. Most are within the stomach. In general, the site of preference is the pylorus or the middle third of the stomach.

About 10 to 12 per cent of tumors are in the upper third. The tumors may be single or multiple, and occasionally they are numerous. This is especially true of the epithelial tumors, which consist chiefly of adenomatous polyps. The tumors tend to be regularly ovoid, with a rather smooth contour, but sometimes they are irregularly polygonal or multilobular. Intragastric tumors are subject to ulceration, superficial as a rule (Fig. 63). Unlike ulcer and cancer, they are usually situated some distance from the curvatures, often occupying a midposition on the anterior or posterior wall. With the exception of the larger pedunculated exogastric growths, benign tumors of the stomach, even those which produce rather large filling defects on the roentgenograms, are not readily palpable. Whereas ulcer and cancer predominantly affect the male sex, benign tumors are found as frequently among women, if not more so.

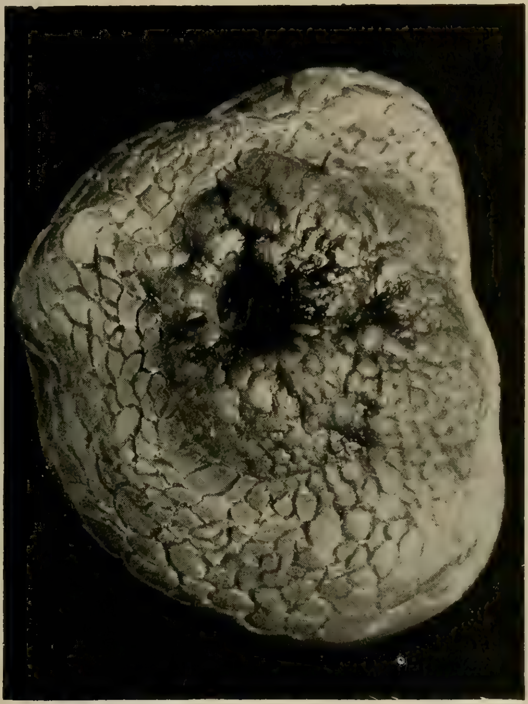

Fig. 63.—Crater on ulcer on a benign tumor. (Eusterman and Balfour, *The Stomach and Duodenum*; courtesy of W. B. Saunders Company.)

Histologic Characteristics.—The histologic appearance of benign new growths of the stomach varies widely. The classification of the tumors in 176 cases observed at the clinic is shown in Table 5. In all these cases the tumor was removed at operation and examined histologically. I have purposely excluded such conditions as pancreatic rest, phytobezoar, hypertrophic pylorus of adults, hypertrophic mucosa, fibromatosis, gumma and hypertrophic polypoid gastritis, which are sometimes classified with benign tumors.

SYMPTOMS

The unobtrusive, symptomless nature of the majority of benign gastric tumors is a matter of common observation. This is largely due to the fact that the motor and the secretory function of the stomach are not interfered with unless the tumor is situated at or proximal to one of the orifices. A large tumor, even though centrally situated, may at times give rise to vague epigastric pain or discomfort and a sense of fulness in that region after meals and sometimes may cause diarrhea. Otherwise, in the absence of associated lesions in the stomach, duodenum or other abdominal organs, the symptoms are usually the result of some complication like gross or occult bleeding, intermittent pyloric obstruction, intussusception or malignant transformation. With the possible exception of perforation, a benign tumor undergoes the same complications or transformation as a gastric ulcer, and may cause intussusception as well. On that account the appellation benign is in the strict sense a misnomer.

Gastroenteric hemorrhage and the symptoms arising from a marked anemia are the most frequent and significant manifestations. The incidence of anemia and occult bleeding seems relatively greater in cases of benign tumor of the stomach than in cases of peptic ulcer. While the anemia is usually of the so-called secondary type, an increasing number of cases in which primary or macrocytic anemia occurs in association with polypoid gastric lesions is coming under observation at the clinic.

Contrary to the opinion of some writers, there is no characteristic syndrome in my judgment. Bleeding in the absence of pain or dyspepsia can occur in a variety of lesions or conditions intrinsic or extrinsic to the stomach. Myomatous tumors or juxtapyloric adenomatous polyps frequently simulate duodenal ulcer. The subjective symptoms engendered by severe anemia are often the only presenting complaint, explaining the rationale of excluding the digestive tract as a source of trouble in all cases of obscure anemia. The painful, prostrating phenomena of intussusception invariably go unrecognized or are erroneously attributed to biliary colic or acute perforation of an ulcer because of the rarity of the condition. Symptoms or signs of pyloric obstruction occur in 10 to 15 per cent of cases.

A considerable number of these tumors, especially the smaller ones, always will be found at operation, because of their occasional association with gastric carcinoma and ulcer, duodenal ulcer or cholecystic disease which necessitates operation. Obviously, any symptoms engendered by such tumors would be over-shadowed by the symptoms produced by the latter types of lesion. Dyspepsia is noted in some form in about 20 per cent of cases in the absence of other lesions. Symptoms or signs suggestive of carcinoma are not uncommon, because certain features are common to benign and malignant lesions, such as age (average age, fifty-four years), loss of weight, anemia, achlorhydria, evidence of tumor and occasionally undue retention of the gastric contents owing to mechanical obstruction at the outlet of the stomach.

DIAGNOSIS

The first consideration, of course, is whether the neoplasm is malignant or benign. In the last analysis this can often be determined only histologically. Clinical features which may be of value in distinguishing benign from malignant gastric tumors are: (1) The incidence of benign tumors is low; because of the great preponderance of malignant tumors the law of averages would largely favor the diagnosis of carcinoma when there is any reasonable doubt. (2) With benign tumor, symptoms of indigestion are absent or mild; moreover, the nutritional state is good; obstruction rarely occurs and a palpable mass is seldom found. (3) With benign tumor, anemia and gastroenteric hemorrhage are the outstanding, and often the only, symptoms or signs; gross hemorrhage is unusual with malignant gastric tumor, especially early in its course. Secondary anemia, not infrequently a primary form, in the absence of hemorrhage may be the only feature noted in cases of benign tumor; in fact, anemia, as previously has been stated, is the most common sign. (4) Some patients with benign tumor are young; several of the largest of such tumors were found in children. On occasion the only physical findings suggestive of benign tumor occur when the growth is palpable. Final differential diagnosis is dependent on roentgen or gastroscopic examination or both.

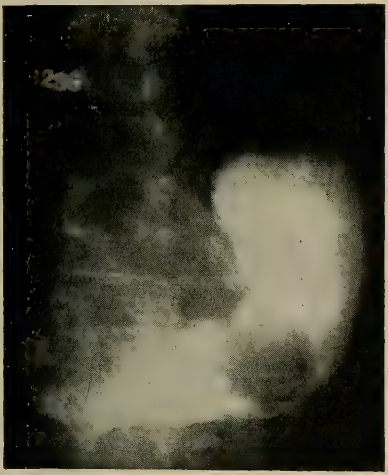

Fig. 64

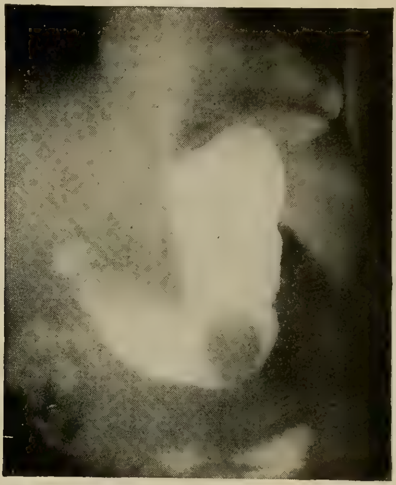

Fig. 65

Fig. 64.—Large filling defect of the middle portion of the stomach, typical of a benign tumor. (Eusterman and Balfour, *The Stomach and Duodenum*; courtesy of W. B. Saunders Company.)

Fig. 65.—Large round defect in the middle portion of the stomach, produced by extrinsic pressure from a cyst of the pancreas. (Eusterman and Balfour, *The Stomach and Duodenum*; courtesy of W. B. Saunders Company.)

As the symptoms and the results of analysis of the gastric contents often afford little concrete aid, one must resort to visual or objective methods, particularly roentgenoscopy. Through improvements in roentgen technic, chiefly close and complete manual approximation of the partly and completely filled stomach with the contrast meal and deep penetration, many benign neoplasms, formerly overlooked, are now discovered. Moore[23] pointed out that a benign gastric tumor usually produces a centrally situated (Fig. 64) and clearly circumscribed filling defect. This does not distort the rugae, interfere with peristalsis, obstruct the pylorus (unless situated in the antrum) or cause any contraction or spasm of the stomach.

Moore wisely concluded that such growths, especially pedunculated ones, may be primarily or secondarily malignant. Kirklin[16] said that the roentgenologist may have to consider food remnants in the stomach, bezoars, extrinsic tumors like pancreatic cysts (Fig. 65), spastic crenulations of the greater curvature, simple hypertrophy of the gastric rugae, hypertrophic gastritis and, of course, malignant new growth. In doubtful cases, gastroscopic examination furnishes complementary and often decisive information as to the nature and extent, superficial appearance and exact situation with reference to the walls, whether anterior or posterior. Schindler, Sandweiss and Mintz[31] described, as characteristic of a submucosal tumor, stretching of one or more mucosal folds from the surrounding mucosa up to the surface of the tumor, apparently bridging the space between the summit of the tumor and the level of the surrounding mucosa. Moreover, single or multiple polyps may be distinguished from hypertrophied rugae, inflammatory pseudopolyps and hyperplastic polyps. Peritoneoscopy has been helpful in the identification of pedunculated exogastric tumors.

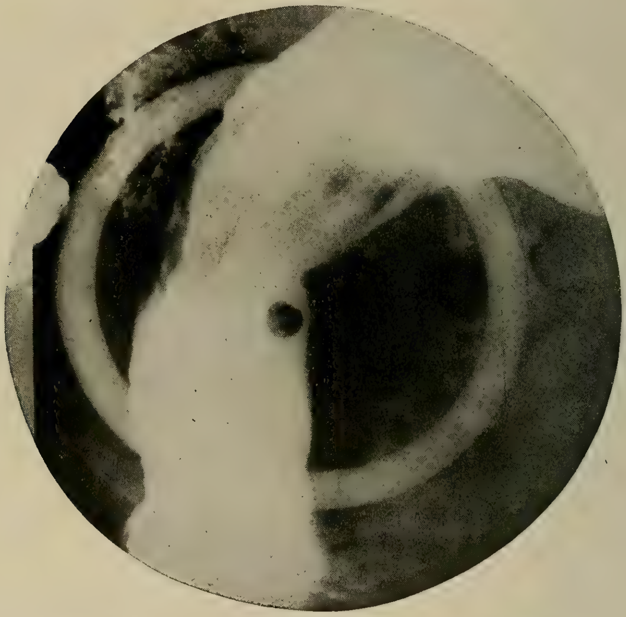

Fig. 66.—Round defect produced by small benign polyp.

TYPES OF TUMORS

Polyp.—Exception has been taken to the term "polyp," because it is descriptive of a gross physical rather than of a histologic characteristic. By this expression, however, is meant a benign adenomatous, rarely papillomatous, tumor. The former type is the commonest of all benign tumors, and is of etiologic, clinical and pathologic significance.

In a little more than half of the cases the polyp occurred singly (Fig. 66). In the remainder two or more polyps were noted (Fig. 67). They vary in size from 6 millimeters in diameter to 8 centimeters long by 2.5 centimeters wide. The sites of predilection are the posterior wall, in the pyloric region, and perhaps less frequently the anterior wall. This tumor occurs more commonly than any other benign tumor with other gastric lesions. Polyps are considered to be of either congenital neoplastic or inflammatory origin. Each type has certain gross and microscopic characteristics by which it may often be identified.[3,26,33] As most polyps are associated with achlorhydria, anemia of either hypochromic microcytic or macrocytic form and gross and microscopic evidence of inflammatory changes in the gastric mucous membrane, it is difficult to deny the role that mucosal inflammation or retrogressive change, however engendered, plays in their origin. On the basis of gastroscopic observations Schindler[30] concluded that mucosa affected by atrophic gastritis has seven times greater predisposition to benign adenomatous polyps than the normal mucosa.

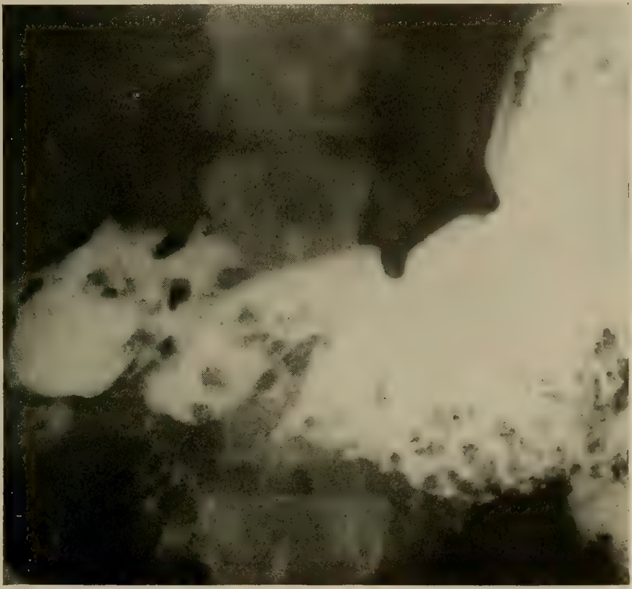

FIG. 67.—Round defect produced by multiple discrete polyps, *polyadenomes polypeux*.

Polypoid forms of carcinoma have been associated often with polyps at the clinic. Moreover, carcinoma often developed at the site of the excision, by knife or cautery, of an apparently benign polyp. McRoberts[21] emphasized that these adenomas are prone to malignant changes, and he reported 5 cases, in 4 of which malignant changes could be demonstrated in the tumor. Hartman and Camp[14] reported a small malignant gastric polyp associated with a large exogastric leiomyoma, for which operation was successfully carried out. The patient died eventually of extensive recurrence.

Haring[12] cited reports of 41 cases of benign polyps associated with pernicious anemia. Washburn and Rozendaal[39] recently reported 8 cases observed at the Mayo Clinic. Priestley and Heck[27] reported 3 cases of pernicious anemia in which malignant gastric polypoid lesions were present. It it difficult to escape the conviction that the gastric mucous membrane in such cases either is subject to chronic irritation from some source or is easily susceptible to it and that this results in chronic diffuse inflammatory and polypoid changes along with atrophy of the gastric glands and loss of Castle's intrinsic factor. Therefore, such a sequence of events can culminate in pernicious anemia and related macrocytic forms of anemia, in gastric carcinoma or in both grave anemia and carcinoma. In other instances, there may be no marked hematologic changes in spite of consistent achlorhydria, or a hypochromic microcytic anemia may develop largely as the result of recurrent gross or occult bleeding. On the relation of anemia to gastrointestinal lesions, the articles by Minot[22] and by Sturgis and Goldhamer[35] furnish an original and inclusive treatment.

Leiomyoma, Fibromyoma, Adenomyoma and Myxofibroma.—The pure and mixed forms of smooth muscle tumor constitute a fourth of the total number of benign tumors observed at the clinic. These tumors were exceeded in frequency only by adenomatous polyps. Many writers consider leiomyoma the commonest form of benign tumor. Collins and Collins[4] stated that of 1,347 benign gastric tumors reported in the available literature, 39.9 per cent were leiomyomas, either pure or containing various amounts of fibrous tissue. I have already cited Rieniets'[28] observations confirming the high incidence of these lesions on careful postmortem examination. The literature contains numerous articles reporting one or more cases. In all likelihood the larger myomas are more frequently the sole cause of operation than are polyps (Fig. 68). Many of the latter, especially the smaller ones which occur singly, have been discovered in the course of operation which was undertaken primarily for other gross lesions of the stomach or duodenum.

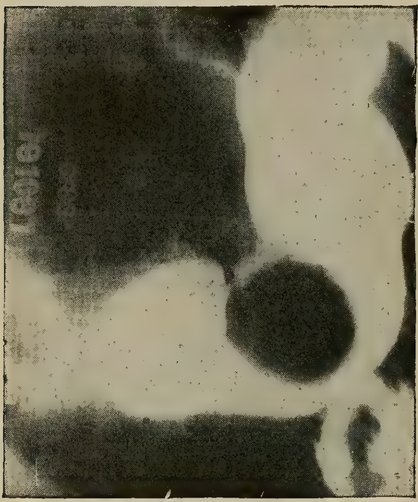

FIG. 68.—Large filling defect on posterior wall of the stomach, produced by palpable myoma. (Eusterman and Balfour, *The Stomach and Duodenum*; courtesy of W. B. Saunders Company.)

Leiomyoma may be situated anywhere in the digestive tract, from the esophagus downward. Sarcomatous transformation is not uncommon, although most observers are agreed that the tendency to such transformation is greater among tumors of the intestinal tract than among tumors of the stomach. The clinical and pathologic details concerning leiomyoma and its congeners will be found elsewhere.[32]

Adenoma.—Adenomas other than adenomatous polyps comprised about 10 per cent of the benign tumors in my series. These tumors varied from a fraction of a centimeter to 6 centimeters in diameter. One of the earliest tumors of this nature to come under my observation was a brunnerian adenoma, a lesion first described by Hayem. It was 2.5 by 1 centimeter, situated about 1 centimeter above the pylorus. It apparently was symptomless and was discovered and excised during the course of an operation for a diseased gallbladder. In some cases the symptoms may be suggestive of ulcer, especially if the tumor is juxtapyloric. One patient had marked anemia and had been treated for pernicious anemia.

Polyposis.—Ten cases of this interesting lesion have come under my observation so far. Balfour's[1] report, in which the lesion corresponded to Menetrier's second variety, *polyadenomes en nappe,* is characteristic. The small growths are packed in orderly rows and macroscopically resemble the convolutions of the brain (Fig. 69). Because "gastric polyposis" is a term loosely applied to a condition marked by various multiple intragastric polypoid growths, Broders suggested that the entity might better be called "polypoidosis" to avoid confusion. The roentgenologic and pathologic aspects of this type of tumor have been described at greater length by Kirklin and Broders.[17]

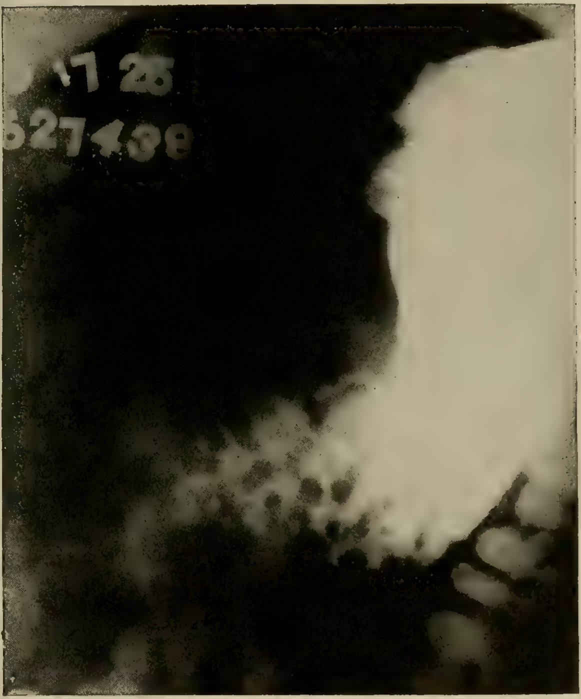

Fig.—69.—Extensive polyposis of the pyloric half of the stomach (the polyadenomes *en nappe* of Menetrier). (Eusterman and Balfour, *The Stomach and Duodenum*; courtesy of W. B. Saunders Company.)

Hemangioma.—This tumor is of interest because of its comparative rarity, fair size and great tendency to bleed or to cause anemia, and because it never undergoes malignant changes. The tumors coming under my observation varied from 2.5 to 6 centimeters in diameter; the largest weighed 108 Gm. With one or two exceptions the tumors were round and sessile and were very mobile at operation. They were situated between the mucosa and serosa and were soft and bluish black or red (Fig. 70).

Fibroma.—Fibroma does not occur as frequently as one would expect. It is usually situated in the region of the pylorus and does not attain any appreciable size as a rule. It occasionally gives rise to symptoms and signs strongly suggestive of duodenal ulcer or pyloric carcinoma with obstruction. No malignant changes were observed in the 6 cases in my series.

Neurofibroma.—In recent years 5 cases of neurofibroma of the stomach have come under my observation. Neurofibroma is the rarest of benign gastric tumors.[25] Van Gelderen[37] recently reported a case of melena and cramps in the upper part of the abdomen. A roentgenogram disclosed a characteristic round, smooth filling defect and a niche *en face* indicative of ulceration. Sympathoblastomas—that is, tumors of neurosympathetic origin—also have been reported recently.

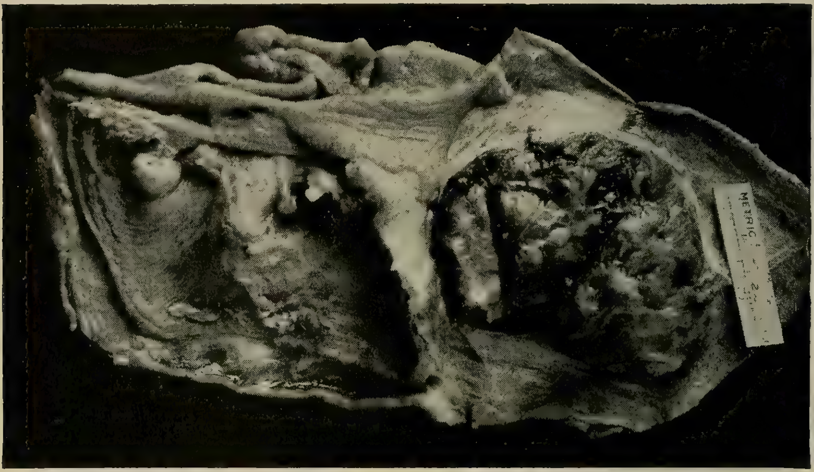

FIG. 70.—Gross specimen of benign angioma of the stomach. (Eusterman and Balfour, *The Stomach and Duodenum*; courtesy of W. B. Saunders Company.)

Dermoid Cyst.—Seven varities of cyst, representing 5 to 6 per cent of all benign tumors, have been commonly described.[7] These varieties do not include cystic degeneration, which is not uncommon in the larger and older tumors of all types. Three cysts which were classified as dermoid were found in my material. They furnished the basis of a report by Gray and Wood.[11] One of my earliest cases was most unusual. The patient was a boy aged eight years, who harbored a cyst weighing 1,000 Gm. and involving the posterior wall of the stomach.

Papilloma.—Contrary to the opinion of some observers, papilloma in my experience is extremely rare. In one of my 2 cases the papilloma of the stomach was associated with multiple tumors of the jejunum, in all likelihood papillomatous, and with a duodenal ulcer. The patient was only moderately anemic. Harper[13] reported a case of multiple bleeding malignant papillomas of the stomach associated with pernicious anemia.

Lipoma.—Gastric lipoma is extremely rare, usually being found at necropsy. It is more frequent in the intestine than in the stomach. In the stomach lipomas range in size from that of a hazelnut to that of a walnut. They are usually solitary and rarely undergo cystic or malignant transformation. In my single case, which was reported by White and Judd,[40] a submucous lipoma measuring 5.5 by 3.5 by 2 centimeters was situated on the anterior wall of the stomach, midway between the curvatures. This tumor has given rise to recurrent attacks of melena for five years. I have found several other symptomless lipomas at necropsy, but these have not been included in this series.

TREATMENT OF BENIGN TUMORS OF THE STOMACH

Once the diagnosis of gastric tumor has been established, the treatment is primarily surgical. Even when the symptoms are not urgent, operation cannot always be safely deferred, because of the threat of hemorrhage or malignancy. This is particularly true of polypoid lesions, which are all potentially malignant. Formerly, owing to physicians' lack of familiarity with these tumors, a certain number of patients were refused operation because of the extent and unfavorable situation of the tumors, which were assumed to be carcinomatous. It was only on the insistence of the patient that operation was performed and the benign nature of the lesion discovered as a result. In many of the earlier series of cases of primary and benign tumors, the neoplasm was discovered in this manner.

Only rarely is a benign gastric tumor so situated that it cannot be removed, and in the majority of cases local excision rather than resection is indicated. The situation of the tumor determines the best method of approach. The procedure used most frequently at the clinic was transgastric excision, performed through an incision in the anterior wall, and division of the pedicle by cautery. An alternative conservative procedure is resection of that segment of the stomach which contains the tumor. In cases of large tumor, the possibility of malignant transformation makes partial gastrectomy advisable. In Walters'[38] opinion, gastrectomy is also desirable for the removal of multiple polyps if one can include the polyps in the portion of the stomach excised. Of course, gastric resection is also imperative whenever microscopic examination of a tumor removed by excision or sleeve resection reveals malignant changes. Preoperative preparation is frequently necessary to combat anemia or to correct the toxemia and dehydration which occasionally result from pyloric obstruction or intussusception. The surgical end-results should be excellent and the mortality low.

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CHAPTER XIV

SYPHILIS OF THE STOMACH

Until recently it has been generally believed and taught that the lesions of acquired syphilis of the alimentary tract were confined almost entirely to the mouth, nasopharynx and anorectal tissues. But in the light of an accumulation of authoritative serologic, bacteriologic, clinical and pathologic observations, it is apparent that the esophagus, stomach, small intestine, colon and rectum are only relatively immune. In acquired syphilis of the alimentary tract, the stomach appears to be the commonest site of late lesions. Next in order of frequency, the esophagus, small intestine, colon and rectum are involved.

It is reasonable to presume that routine serologic and roentgen examination of patients who have gastrointestinal disturbances had led to the eventual disclosure of gastric or intestinal lesions of syphilitic origin and to a clearer comprehension of their incidence among living persons, just as roentgen examination has led to more frequent preoperative disclosure of benign gastric and duodenal ulcers, gastric tumors, jejunal ulcers, diaphragmatic hernias, diverticula, tumors and inflammatory lesions of the small and large intestine. The difficulty of making an unequivocal diagnosis of acquired visceral syphilis in many instances is generally appreciated, as well as the fact that only rarely are the gastric disturbances of syphilitic patients the result of actual gross syphilitis lesions of the stomach.

No other type of organic gastric disease will so frequently undergo such favorable, sometimes spectacular, transformation in the face of what appears to be a grave situation, provided that the true nature of the lesion is recognized in time and that proper therapeutic measures are instituted. Up to the present writing I have observed more than 115 cases personally. My last published report[5] dealt with a series of 93 cases, on which I have obtained follow-up data for years, in order definitely to exclude other causes, especially carcinoma. The findings and deductions which have been drawn from this study should be applicable to the appraisal of other cases.

INCIDENCE

Chiari[4] (1891) encountered 1 syphilitic gastric ulcer in 89 cases of syphilis in which necropsy was performed. Symmers[22] (1916) found at necropsy only 1 gastric lesion that was undoubtedly syphilitic among 314 cases in which there were late lesions of acquired syphilis. (From a clinical standpoint, Chase expressed the opinion that about 1 out of every 1,000 patients who have syphilis has a gross syphilitic lesion of the stomach.) McNeil[10] made a diagnosis of 2 such lesions in 1,200 cases of syphilis. Stokes[21] (1934) cited Moutier as finding 8 such lesions in 8,000 cases of gastric disorder. O'Leary[17] (1931) found gross syphilitic lesions of the stomach in 89 of 25,000 cases of syphilis. Warthin[23] took Symmers to task for his paucity of findings by stating that the latter based his observations on the gross pathology of prespirochetal days, which recognized the gumma as practically the only anatomic lesion of syphilis. Warthin's observation may be the chief reason for the discrepancy between the incidence of lesions seen at necropsy and the greater incidence of gastric syphilis demonstrated clinically.

As to the racial and geographic incidence of the disease, Boas[2] in 1924 cited Galloway as having observed that gastric syphilis is common in China. Aoyama[1] in 1922 said that 4 per cent of the gastric resections that he had performed were necessitated by syphilis. The incidence of the disease in the different countries of Europe in order of probable frequency is as follows: Russia, France, Austria, Germany and England.

Sex and Age.—Of the patients with gastric syphilis who have come under my observation, 70 per cent were men and 30 per cent were women. In 88 per cent the age is between twenty-nine and forty-eight. About half of the patients were between thirty and forty. The average age of the men was thirty-nine years and six months, and that of the women, thirty-six years and six months. The average age of patients of either sex with gastric syphilis when first seen at the Mayo Clinic is about five years less than that of patients with gastric or duodenal ulcer and about twelve years less than that of patients with carcinoma of the stomach.

PATHOLOGY

Congenital syphilis or heredosyphilis as it affects the stomach figured more prominently in the early than in the later literature. Many of the observations were made during necropsy on stillborn or newborn infants and were not recorded in detail. In the majority of cases the gastric lesions were multiple, variable in location, proliferative and infiltrative, and superficial mucosal ulceration occasionally occurred. Gross syphilitic lesions of other organs were usually present.

The gross appearance of the syphilitic stomach at operation has been described by Meyer and Singer,[12] Priestley and Walters[19] and McPeak.[11] Meyer and Singer expressed the belief that the gross characteristics of the lesion are more diagnostic than the histologic ones. They called attention to the thick, boggy, hyperemic wall, which usually is pliable in regions where marked infiltration should have been present if the corresponding changes in the roentgenogram were any criterion. In gastric carcinoma the process is usually more extensive than the roentgen findings would lead one to believe. In gastric syphilis just the reverse obtains. Meyer and Singer called attention also to rarity of perigastric adhesions, the presence of soft, slightly enlarged regional lymph nodes, and telltale gummatous involvement or scarring of the liver.

The microscopic appearance is somewhat dependent on the type and stage of the syphilitic lesion. Like the gross and roentgen appearance, the histologic architecture, according to most pathologists, is nonpathognomonic for syphilis. Warthin,[23] a serious student of visceral syphilis and a pathologist of wide experience, called the essential lesion of either late or latent syphilis an irritative or inflammatory process of variable degree which is characterized by lymphocytic and plasma cell infiltration in the stroma, particularly about the blood and lymphatic vessels (Fig. 71). Small single or conglomerate gummas or gummatous nodules are occasionally encountered (Fig. 72). Fibroblastic and other histiocytic proliferations and vascular lesions in the nature of proliferating endarteritis and panphlebitis, especially in the form of periendophlebitis, are commonly present. In advanced stages the histologic picture shows chiefly marked fibrosis of the thickened muscularis, hypertrophy of the submucosa and atrophy of the mucosa.

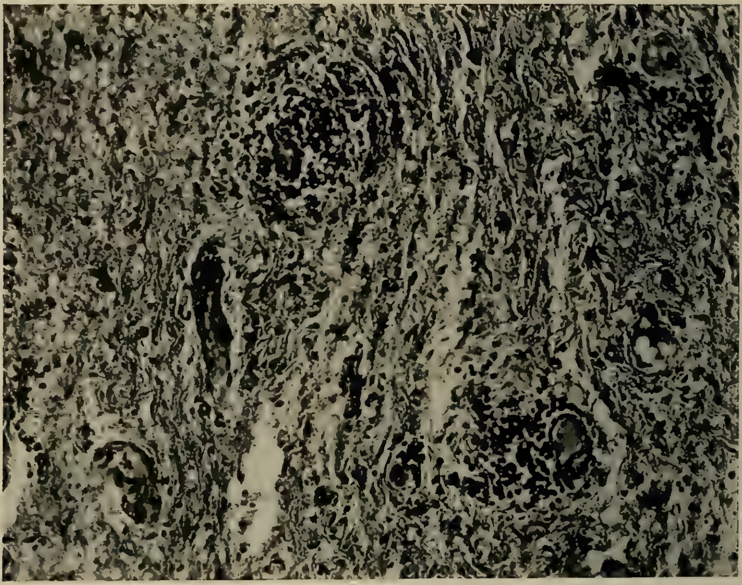

Fig. 71.—Specimen from the edge of one of a group of multiple shallow gastric ulcers in a case of syphilis of the stomach. Moderate fibrosis and perivascular infiltration with plasma cells and lymphocytes are seen (× 120). (Eusterman and Balfour, *The Stomach and Duodenum*; courtesy of W. B. Saunders Company.)

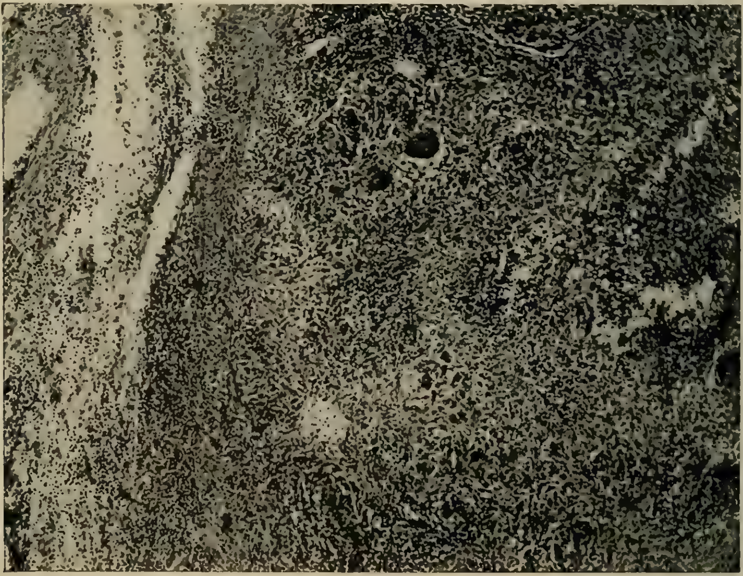

Fig. 72.—Conglomerate gummas with central necrosis and dense lymphocyte and plasma cell infiltration. A few foreign body giant cells are present (× 110). (Eusterman and Balfour, *The Stomach and Duodenum*; courtesy of W. B. Saunders Company.)

The pathologic anatomic picture of acquired gastric syphilis usually involves the pyloric antrum to some degree. Then in order of frequency the middle portion and the entire stomach are affected. Such generalized or diffuse involvement frequently characterizes advanced syphilis or congenital syphilis in which the patient may survive to early adult life. Tumefaction, pyloric obstruction and demonstrable discrete ulcerative processes, common with gastric carcinoma, are much less frequent with authentic gastric syphilis. The essential lesion of the late stages is of chronic inflammatory nature, causing induration and thickening of the gastric wall (Fig. 73). The process, which begins in the submucosa, is usually annular, occasionally diffuse. With untreated syphilis there are progressive reduction of gastric capacity, narrowing of the gastric lumen and secondary superficial ulceration of the gastric mucosa.

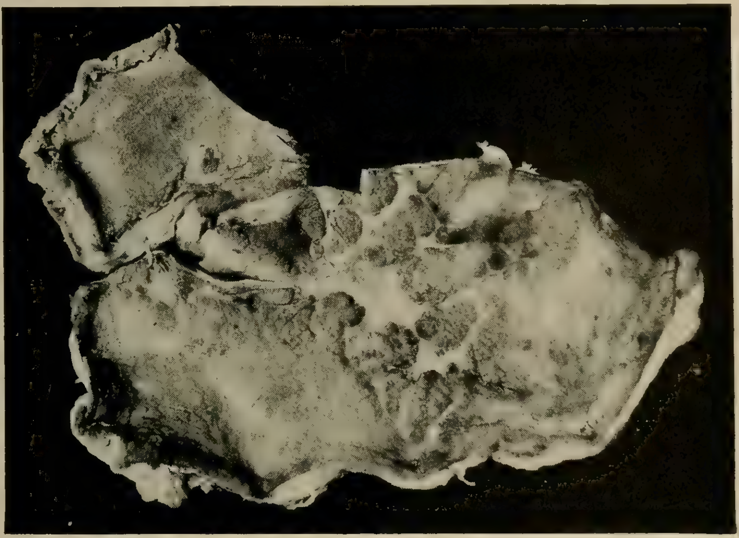

Fig. 73.—Gastric syphilis with multiple serpiginous ulcers. (Eusterman and Balfour, *The Stomach and Duodenum*; courtesy of W. B. Saunders Company.)

SYMPTOMS

Almost two-thirds (63 per cent) of the patients said that epigastric pain or discomfort, which had come on immediately after eating, had been the first symptom. Increase in solidity or amount of food or fluids had caused proportionate increase in discomfort. One feature common to all 93 patients was the progressively severe nature of the clinical course; the majority were in a state of partial or advanced starvation by the time they were observed at the clinic. They were partaking only of liquid nourishment, in reduced amounts and necessarily at frequent intervals. In the advanced stage, the syndrome in the majority of this major group of two-thirds of the patients was that of a stomach reduced greatly in capacity, like the stomach seen in cases of linitis plastica. This syndrome was not necessarily limited to cases in which the stomach was severely contracted, but occasionally was seen with obstructing lesions in the prepyloric region, the familiar site of syphilis, without marked extension of the process upward. Vomiting and pain were outstanding, but nausea and anorexia, except in advanced disease with extensive involvement of other viscera, usually were absent or were much less in evidence than in cases of carcinoma. Cases of hour-glass contraction involving the upper third of the stomach are included in this group of 63 per cent. Usually the symptoms were progressively severe.

In 15 per cent of the 93 cases the syndrome was of the pseudocancer type. The symptoms were of gradual onset. There was mild discomfort at the outset; this appeared about half an hour after meals. If relief after taking food was obtained, it was inconstant or incomplete. The postprandial pain or discomfort gradually became more marked and appeared sooner than it has formerly; the clinical picture gradually merged, as a rule, into that of the first type, with increasing loss of weight and strength, and the symptoms were more easily affected by the degree and character of the ailment.

In another group of cases, which comprised 22 per cent of this series, the syndrome was classified as the ulcer type. In this group, the "pain-food-ease" sequence seen in cases of ulcer was outstanding throughout the whole, or part of, the duration, although the sequence was not so regular or so complete as in cases of duodenal ulcer. As the condition progresses, some of the cases in this group eventually had to be classified in the first or the second group. In 8 cases, probably because of an incomplete history, there seemed to be complete absence of pain or epigastric distress.

Obviously, there are no pathognomonic or characteristic symptoms, and the symptoms are often too nondescript to permit satisfactory classification. Nevertheless, one should at least be mindful of the symptoms which have been described, and which are characteristic of 63 per cent of the cases, and of their possible significance, especially in the presence of other clinical or serologic evidence of syphilis. Gastroenteric hemorrhage is an infrequent complication. While acute perforation of the stomach has been reported by other observers, there was no evidence of this complication in any of the 93 cases. Frequently an associated hepar lobatum or syphilitic cirrhosis, with the resulting esophageal or gastric varices, is the underlying cause of the hemorrhage. Hemorrhage is more characteristic of ulcer and of carcinoma of the stomach, especially the former, than it is of syphilis. Anemia was present in only 14 cases. This was of the secondary type and usually was not marked.

Results of Analysis of Gastric Contents.—In 22 (24 per cent) of the 93 cases, there was gross retention of gastric contents. This was chiefly the result of obstruction from prepyloric involvement or occasionally from hour-glass contraction of the middle or upper third of the stomach. A palpable mass was present in only 20 per cent of cases, and a definite sense of resistance was present over the region of involvement in most patients who were thin and dehydrated. Achlorhydria was present in 85 per cent of the 93 cases. This is a higher percentage than I have encountered with any other type of gross disease of the stomach. In some of the cases that have been observed recently, the use of histamine failed to stimulate secretion of free hydrochloric acid. However, I have noted records of 4 cases in which the free hydrochloric acid, consistently absent before treatment, returned afterward.

Results of Serologic Tests.—The Wassermann reaction of the blood serum, of the spinal fluid or of both was positive in 92 per cent of the 93 cases. It was negative for the blood serum in 7 cases; 3 of these were cases of heredosyphilis. In 6 cases the test was not made, for the patients came under observation before the Wassermann test was available. O'Leary[17] found that the Wassermann reaction of the spinal fluid was positive in 11 of 89 authentic cases of gastric syphilis.

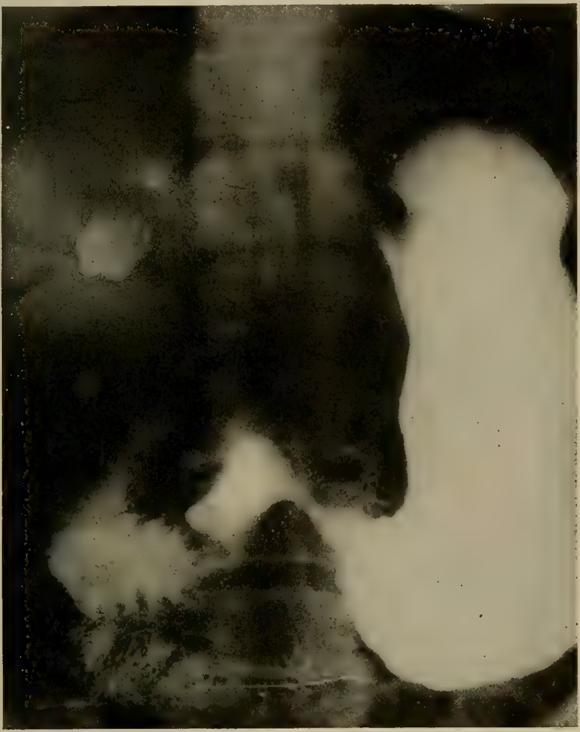

Fig. 74.—Prepyloric defect, result of a gummatous tumor which produced pyloric obstruction. (Courtesy of *American Journal of Syphilis.*)

Results of Roentgen Examination.—In the cases observed at the clinic the lesion was situated in the prepyloric region or the median portion of the stomach, or there was diffuse involvement. In approximately three-fourths of the cases the lesion adjoined the pylorus, from which is extended proximally in varying degree. The roentgenologic defect was almost invariably concentric and symmetric, and the spicular or tubular lumen was relatively smooth (Fig. 74). In almost a fifth of the cases the lesion affected only the middle third of the stomach and produced a dumbbell deformity with a long, central, smooth tubular constriction (Fig. 75). In less than a tenth of the cases the involvement was diffuse, affecting almost all of the stomach but least marked in the cardia. As a result, the greater portion of the stomach was converted into a slender tube, but usually was not shortened (Fig. 76). In all three varieties obstruction is rare, peristalsis is absent from the affected segment and as a rule the barium flows freely and continuously through the pylorus. Important among indirect signs is the almost invariable absence of a definitely palpable mass in the affected segment.

Dumbbell deformity of the stomach, of the character described, is rather characteristic of syphilis but is encountered only in small minority

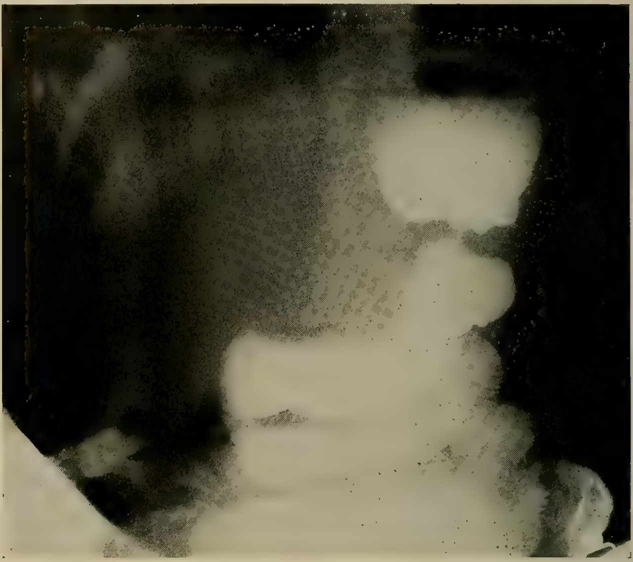

FIG. 75.—Syphilitic hour-glass stomach. (Courtesy of *American Journal of Syphilis.*)

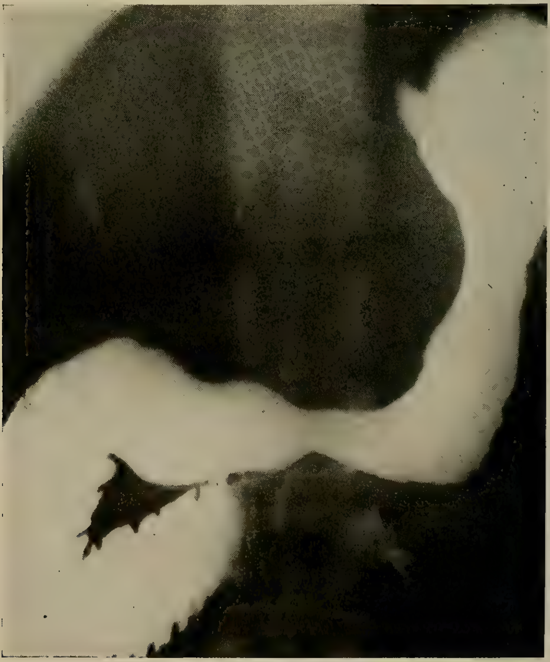

FIG. 76.—Gastric syphilis with diffuse involvement. (Moore and Aurelius, *American Journal of Roentgenology.*)

of cases. In most instances the lesion is likely to be mistaken for scirrhous carcinoma. Certain circumstances, however, should prevent this assumption: 1. The absence of a palpable mass is more or less contradictory of cancer. 2. The patient is often younger than the patient commonly affected by cancer. 3. As a rule, the patient is not markedly weakened or cachectic and is not as ill in proportion to the extent of the lesion as he probably would be if he had cancer. All or any of these observations in conjunction with smooth tubular concentric narrowing of the stomach constitute a sufficient basis for a tentative roentgenologic diagnosis of syphilis, subject to further clinical and laboratory investigation.

Results of Gastroscopic Examination.—Moutier[14] divided the cases into those of tumor (gumma) formation leaving a localized scar on healing; those of single or multiple ulcers which leave residual scars on healing but are associated with more contracture and deformity (hour-glass contraction) of the stomach, and those of generalized gastritis, often hemorrhagic, which results in a leather-bottle stomach or linitis plastica that simulates scirrhous carcinoma. The appearance of the lesions was illustrated by colored plates.

Kerkhof[8] described the gastroscopic appearance of a large ulcerous gastric lesion which had the histologic characteristics of a late syphilitic lesion and which, while under gastroscopic observation, healed after antisyphilitic treatment, with the formation of residual scar tissue. Gutzeit and Teitge[6] and Carey and Ylvisaker[3] described the appearance of the gastric mucous membrane of syphilitic persons who did or did not have gastric disturbances. Moersch[13] had an opportunity to observe 1 case in which hypertrophic polypoid changes in the stomach practically disappeared as a result of treatment. Palmer, Schindler, Templeton and Humphreys[18] reported the case of a man aged thirty-six, in whom it was impossible to make a differential diagnosis between gastric syphilis and ulcerating carcinoma on gastroscopic examination.

Gastroscopic examination should be extremely helpful not only in differentiating syphilitic ulceration from the ordinary chronic variety but in supplying valuable information as to the effect of antisyphilitic treatment on such lesions or on other mucosal abnormalities.

DIAGNOSIS

The majority of the patients are in the third to the fifth decade of life, and the average age, irrespective of sex, is about thirty-seven years and six months. Gastric disturbances usually are marked and progressive and have an average duration of two years. Symptoms depend in large degree on the site and extent of the lesion and on the existing complications. Achlorhydria or subacidity, especially the former, is the rule. A palpable mass, retention of gastric contents, nausea, anorexia, anemia, cachexia, gross hemorrhage and occult bleeding are infrequent, in contrast to their incidence in carcinoma, for which the laboratory data usually simulate those for gastric syphilis. The diagnosis often is inferential because of the frequent absence of a palpable mass corresponding to the position of a filling defect and because of the disproportion between the general condition of the patient and the extent of the gastric involvement as revealed by roentgenoscopic examination.

Clinical versus Pathologic Diagnosis.—Most pathologists, and a few surgeons, do not regard as authentic any diagnosis of gastric syphilis without histologic or bacteriologic confirmation. This naturally presupposes laparotomy or necropsy in every instance. These same pathologists insist that no histologic findings can be regarded as pathognomonic of the disease and that bacteriologic methods are unreliable. I agree with them that a considerable number of the clinical reports are unacceptable because of the lack of sufficient evidence. But to persist in the attitude of excluding all cases in the light of accumulated knowledge is indicative of a woeful lack of diagnostic acumen and therapeutic resourcefulness, in my opinion.

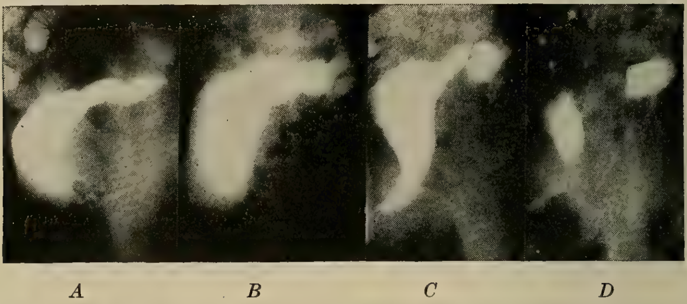

Fig. 77.—Progress of gastric syphilis in a woman, aged thirty years: *A*, Sept. 20, 1915, filling defect at the pyloric antrum is seen; a palpable mass or retention was not present; *B*, Nov. 15, 1915, the condition is much improved; *C*, Oct. 5, 1916, the stomach appears practically normal; *D*, April 19, 1929, slight narrowing and stiffening of the antrum are present; clinical cure has taken place. (Eusterman and Balfour, *The Stomach and Duodenum*; courtesy of W. B. Saunders Company.)

Factors essential to reliable clinical proof of the specificity of the lesion in the absence of pathologic examination are the observation of systemic syphilis, proper appraisal of all subjective and objective data and evaluation of the results of specific therapy. Routine flocculation and serologic tests and systematic physical, neurologic and roentgenologic examinations of every patient suffering from a gastric disorder, coupled with a suspicious attitude on the part of the physician, set the stage for successful diagnosis as well as proper and timely treatment. Most physicians are now familiar with the symptoms, the chemical characteristics of the gastric secretions, the roentgenologic appearance and the therapeutic response which characterize gastric syphilis. Much important fundamental knowledge has been obtained as the result of operations on patients for whom the erroneous diagnosis of gastric carcinoma has been made, and now there is no justification for further indiscriminate operation. Of course in the presence of an unyielding stenosis or when satisfactory clinical exclusion of carcinoma in an otherwise operable lesion is impossible, surgical intervention is justifiable.

The uncompromising attitude of those who insist that no diagnosis of gastric syphilis is proved until the specific organism is demonstrated in the excised or resected gastric tissue is supported by the following facts: 1. It is impossible to distinguish *Spirochaeta pallida* from other spirochetes on microscopic examination of patients in spite of improved tinctorial methods. On this account the case reported by McNee[9] would have to be placed in the doubtful class. 2. As pointed out by Singer[20] and others, saprophytic spirochetes indistinguishable from *S. pallida* may be found in nonsyphilitic ulcerative lesions of the stomach, in a zone bordering the necrotic surface of the ulcer. 3. Inoculation of suspensions of macerated lesions into rabbits is also inconclusive, in the opinion of such an authority as Noguchi,[15] because *Treponema cuniculi,* which is naturally present in rabbit spirochetosis, cannot be distinguished from *S. pallida.* This fact tends to vitiate the conclusions drawn from the experimental observations of Harris and Morgan,[7] but in no wise detracts from the authenticity of the case which these authors reported, in my opinion. 4. When the lesion is advanced it is extremely difficult, if not impossible, to find the organism.

The chief limitation of the therapeutic test is that the fibrous, scirrhous type of syphilitic gastric lesion usually gives no evidence of anatomic restoration or improvement following treatment. Therefore, unless symptomatic improvement is marked and enduring, which is infrequent, satisfactory differential diagnosis on this basis is impossible. Some authors have stated that the results of specific treatment may be misleading in cases of gastric carcinoma, owing to the improvement that follows. In my experience such symptomatic improvement is negligible and anatomic improvement, which is the all-important factor, never occurs in the presence of carcinoma.

It is often difficult to make a decision as to the extent, if any, to which the therapeutic test should be carried in order to distinguish a syphilitic lesion from a carcinomatous one, which, after all, is the major diagnostic problem here. If the lesion appears to be carcinomatous and is obviously inoperable, the therapeutic test can be carried out with impunity for four to six weeks, and reliable evidence as to the exact nature of the lesion secured. Should the lesion be an operable one, even if malignant, exploration, of course, is preferable to the delay of "slow" therapeutic tests, but fortunately antisyphilitic treatment for ten to fourteen days affords crucial information in the majority of cases. At any rate, the chance for cure is jeopardized little on account of the brief delay, and in some instances the patient is in a better condition to withstand the operation.

TREATMENT

Fundamentally the mode of treatment for gastric syphilis is that for any form of late syphilis. In addition, it is sometimes feasible to employ, temporarily, certain dietetic precautions. Treatment is undertaken as a therapeutic test or as a means of cure or relief. With respect to the details of the treatment, O'Leary[16] expressed the following opinion:

> It has been my practice to place these patients in the hospital while undergoing the first few weeks of the therapeutic test because it permits of closer supervision, particularly in regard to their dietetic limitations and variations. Either arsphenamine, or neoarsphenamine, is given in small doses, simultaneously with mercury or bismuth, and potassium iodide. The dose of arsphenamine is maintained somewhat lower than that ordinarily employed. For example, for a woman of 120 pounds (54 kg.), 0.4 gm. of arsphenamine or 0.5 gm. neoarsphenamine should be the maximal dose. The injections of arsphenamine are given at weekly intervals. I still prefer daily injections of succinimide of mercury in doses of $\frac{1}{8}$ to $\frac{1}{6}$ grain (0.008 to 0.01 gm.) because of the more rapid effect of the soluble mercurial preparations when compared with insoluble preparations of bismuth or mercury.
>
> The diet prescribed is that of the general hospital tray, as a rule, differing in that it is divided into six meals instead of three, because the capacity of the stomach

usually is decreased. The general tray as a rule can be given on the third or fourth day after the first injection of arsphenamine. The variations in weight should be recorded daily, estimations of hemoglobin and of number of erythrocytes should be made twice a week, and notations should be made in cases in which a tumor is palpable as to decrease in the size and tenderness of the epigastric mass.

In a case of gastric syphilis in which there are either single or multiple gummas or in which the condition is of the diffuse nodular variety, the response to this regimen usually is phenomenal. In fact, I know of no disease in which the therapeutic effect is more dramatic than it is in gastric syphilis of this type. Within the first week, the patient notes a decrease in distress from eating, and shortly is eager to increase the amount ingested, and although he may be obvious of the limited capacity of the stomach, he can eat moderate amounts with only the discomfort of gastric distention and slight dyspepsia. Gain in weight follows immediately, and a gain of 20 to 30 pounds (9 to 14 kg.) in a month is not unusual, with corresponding increases in concentration of hemoglobin and number of erythrocytes. Decrease in size of the palpable mass follows more slowly.

In the case in which the therapeutic test is positive, estimation of the status of the syphilis elsewhere in the body is then necessary. Examination of spinal fluid, appraisal of the cardiovascular system, and estimation of the status of the liver are advisable. Diffuse hepatitis, gummas, or cirrhosis of the liver have been present in about half of our cases of gastric syphilis. If appraisal of these three systems does not demonstrate syphilitic involvement, treatment of the patient who has gastric syphilis then includes three or four courses of arsphenamine, with corresponding amounts of mercury or bismuth, spread over a period of approximately eighteen months.

The opportunity for observation of the case for two years or more, during which time the treatment for syphilis is continued, permits of repeated examinations, sufficient to eliminate the possibility of gastric cancer.

In the event of pyloric obstruction or hour-glass deformity, it is occasionally necessary to resort to an operation. This usually consists of resection and sometimes a plastic procedure.

Results of Treatment.—Of the total number of patients who have been observed by me, who have undergone operation or treatment for gastric syphilis up to 1931 and who are still living, it has been possible to trace all but 6 until recently; those who have been traced were followed approximately until the time of death. Thirty-two of the traced patients (36.8 per cent) were classified as clinically cured, and 37 (42.5 per cent) were classified as much improved. This makes a total of 79 per cent of the traced patients who were cured or much improved. About 10 per cent were not improved, and the other 11 per cent felt that they had received some benefit. Clinical improvement may be out of all proportion to anatomic improvement. Twelve patients who were not subjected to operation on subsequent examination gave evidence of complete anatomic restoration (Fig. 77).

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CHAPTER XV

LINITIS PLASTICA

(Scirrhous Carcinoma, Scirrhus Ventriculi, Diffuse Infiltrating Carcinoma, Leather-bottle Stomach, Fibromatosis of the Stomach, Malignant Fibrosis)

That syphilis and some inflammatory processes may produce a contracted thickened stomach is likely, but I believe that the term linitis plastica should be reserved for the type which is carcinomatous. My reason for taking this position is that pathologists now universally agree that the disease is carcinomatous. Since 1850 authors have reported the majority of lesions as carcinomatous, and this is the prevailing opinion today. Howard in an excellent review presented 10 cases of his own, in all of which the lesion was malignant.

ETIOLOGY

Innumerable theories have been advocated as to the cause of this disease. In the vast majority of the cases reported there was no history of previous gastric disease. A review of the literature shows that it occurs in males more often than in females, at a 2 to 1 ratio, and is most frequent between the ages of thirty and sixty years.

PATHOLOGY

There are two accepted types, the rare localized form and the more frequently recognized diffuse type involving the entire stomach.

Gross Description.—In the diffuse or generalized involvement the stomach is usually converted into a rigid, contracted, tubular organ occupying a position not unlike that of a narrow tube connecting the esophagus and duodenum. It lacks elasticity and distensibility and has an almost cartilaginous feel. On cutting into it, one is at once impressed by the tremendous increase in the thickness of its walls, often eight to ten times normal. The mucosa presents a grossly irregular surface, which may at times give an almost nodular appearance. Shallow superficial ulceration may or may not be present. In advanced disease the submucosa, muscularis and serosa are entirely replaced by thickened fibrous tissue. Brinton found the submucosa ten to twenty times its normal thickness. The region lymph nodes are sometimes metastatically involved. The adjacent structures, such as the peritoneum, diaphragm, liver, spleen, pancreas and adrenal glands may be involved. Areas of similar pathologic change may be found also in the esophagus, duodenum and colon.

Microscopic Pathology.—The mucosa may appear intact and not involved. The muscularis mucosa in many places may be broken up by islands of connective tissue. The submucosa is much thicker than normal and consists of many coarse bundles of connective tissue fibers extending in various directions and invading the muscle coats. There is complete replacement of all glandular structures of the stomach. The muscularis is invaded by irregular connective tissue strands radiating from the submucosa and containing a large number of irregular deeply stained nuclei; the submucosa contains small or large groups of similar epithelial cells in various stages of degeneration. These epithelial cells are considered by the majority of pathologists to be carcinomatous.

Judd, Larsen and Tilden reported a case in which a large portion of the stomach was removed and careful study of the section by several pathologists revealed suggestive signs of linitis plastica, or, as they called it, 'fibrosing gastric carcinoma." Lymph nodes examined at that time showed no metastatic involvement. Two years later a laparotomy disclosed the presence of "malignant fibrosis" of a portion of the transverse and descending colon, the mesentery and adjacent lymph nodes. Pathologic studies at this time left no doubt as to the carcinomatous character of the lesion. The report of this case is included to show that several competent pathologists could not positively determine whether the gastric lesion was malignant, but subsequent examination would lead one to conclude that the original lesion, as well as that of the colon, was malignant.

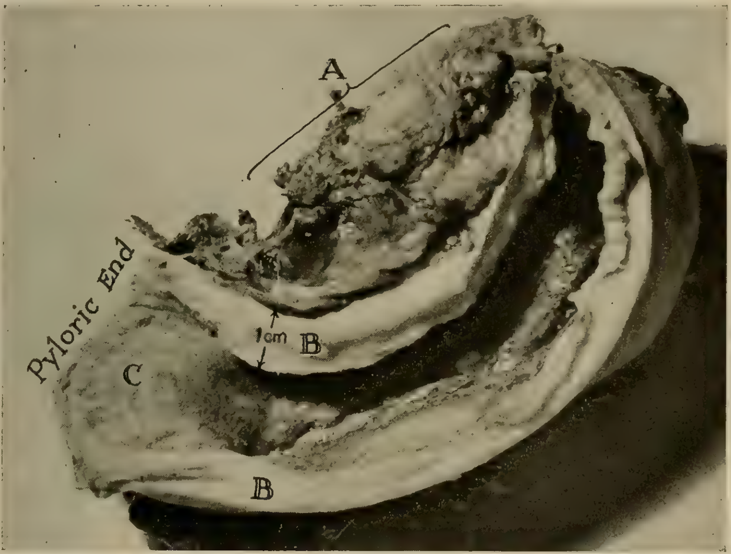

Fig. 78.—Linitis plastica, showing, *A*, metastatic carcinoma in the mesogastric lymph nodes; *B*, stomach wall averaging 1 centimeter thick; *C*, mucosal markings completely lost and capacity greatly decreased.

In the case Wadsworth and I described in 1925, that of a male, the majority of cells assumed the signet ring characteristics which have been described by Krukenberg for so-called Krukenberg carcinoma of the stomach. Frequently the amount of connective tissue makes necessary most diligent search for islets of carcinomatous epithelial cells.

A localized form involving various parts of the stomach but mostly that portion in the vicinity of the pylorus has been described.

SYMPTOMATOLOGY

Eliminating such symptoms as distress and discomfort in the epigastric area, which might be indicative of any disease of the stomach, the first outstanding symptom of linitis plastica is the sensation of complete filling of the stomach by a much smaller total amount of food than the person is accustomed to taking. This, of course, is due to the diminished capacity of the organ. The second characteristic symptom is the regurgitation of food in small amounts, and as the disease progresses actual vomiting ensues, in spite of the fact that the stomach empties rapidly in this disease. This is due to the inability of the ingested material to leave the stomach through the duodenum at an established physiologic rate, resulting in a damming back of the food into the esophagus and its ejection through the mouth. Anorexia is present, and extreme weakness results, owing to starvation. Hemorrhage is rare, owing to the fact that the mucosa seldom is involved by an ulcerating lesion.

PHYSICAL SIGNS

Palpation of the abdomen may reveal a tubular mass in the epigastric area. There is evidence of cachexia and anemia. Metastatic involvement of other structures occasionally occurs, and one may find a sentinel node in the left supraclavicular fossa or involvement of the liver, adjacent lymph nodes or other organs of the abdominal cavity. Ascites is rare, and hydrothorax occurs as a late manifestation.

LABORATORY FINDINGS

Frequently there is achlorhydria due to the destruction of the glandular structure of the stomach. Occult blood is usually not found in the gastric or intestinal contents with this type of carcinoma, owing to the lack of ulceration of the mucosa, in contradistinction to its frequent presence in adenocarcinomatous involvement, which tends to ulcerate and bleed. It should be emphasized that this type of carcinoma involving the stomach without ulceration may be present without the significant finding of persistent occult blood in the stool, so characteristic of other malignant lesions involving the gastrointestinal tract.

Examination of the blood will reveal either a hypochromic microcytic or a hyperchromic macrocytic type of anemia. The deprivation of essential food substances results in a hypochromic microcytic anemia. The hyperchromic macrocytic type is due to a lack of the intrinsic antianemic factor.

X-RAY STUDY

The roentgen examination is the single most valuable procedure to support the clinical diagnosis of linitis plastica. The characteristic evidences are as follows: The cavity of the stomach gives the appearance of a narrow tube with a smooth lining, and one is unable to make out the mucous membrane pattern. The barium meal rushes through the stomach and pyloric outlet into the duodenum. There is an absence of peristalsis. Fluoroscopic palpation reveals that the walls are not pliable.

DIFFERENTIAL DIAGNOSIS

Linitis plastica is confused with syphilis, sarcoma, tuberculosis and rare forms of malignant and benign tumor involving the stomach. Improvement in roentgen technic and the advent of the gastroscope have made it possible to eliminate some of the aforementioned conditions. However, gastroscopy may be of no value, since in some cases it is impossible to distent the stomach with air, which is necessary to visualization. Roentgenologists believe that syphilis of the stomach produces a characteristic deformity which distinguishes it from linitis plastica. Syphilis may be excluded by the absence of involvement of the other structures of the body, negative serologic reactions of blood and spinal fluid, the continued good health of the patient, maintenance of weight, length of life and response to antisyphilitic therapy. Little alteration may occur in the roentgenologic picture after such treatment. The diagnosis of adenocarcinoma is made on the basis of a shorter history of gastric disorder, the characteristic filling

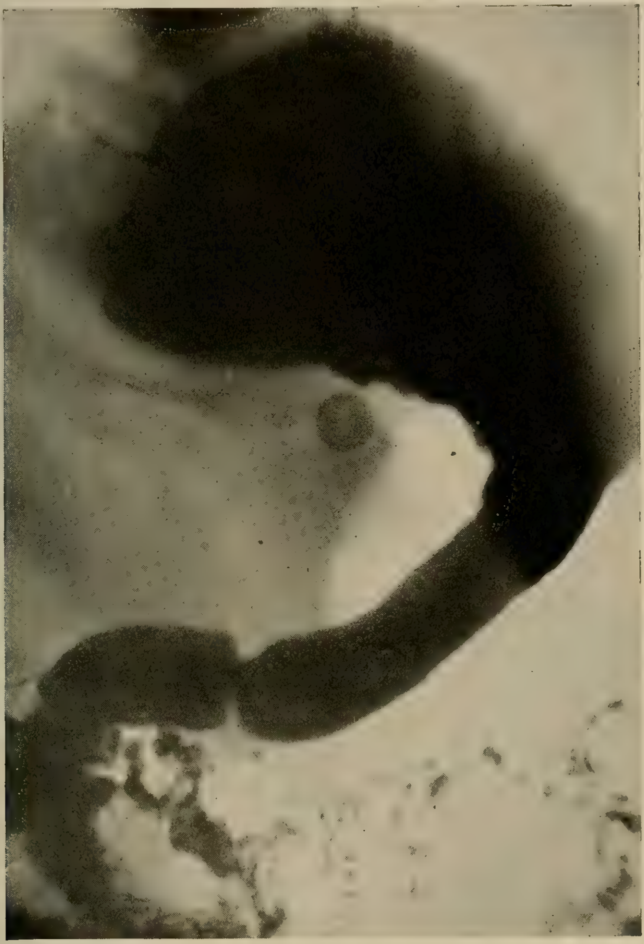

Fig. 79.—Roentgenogram of linitis plastica. The greater portion of the stomach is narrowed down to a rigid tube, and under the fluoroscope gastric peristalsis and pyloric function are absent. The barium meal flows through the stomach and pyloric outlet into the duodenum immediately. The pattern normally produced by the mucous membrane is entirely lost. The entire duodenum and the proximal part of the jejunum generally appear somewhat dilated as the result of over-burdening with the immediate inflow of the barium solution. (Courtesy of Dr. E. C. Koenig.)

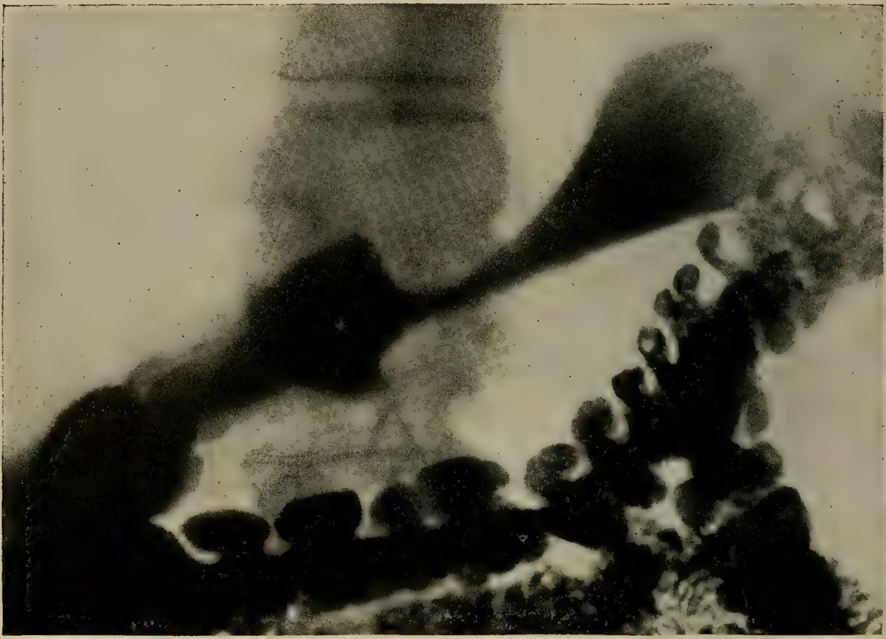

Fig. 80.—Roentgenogram of linitis plastica. (Courtesy of Dr. M. J. Helminiak.)

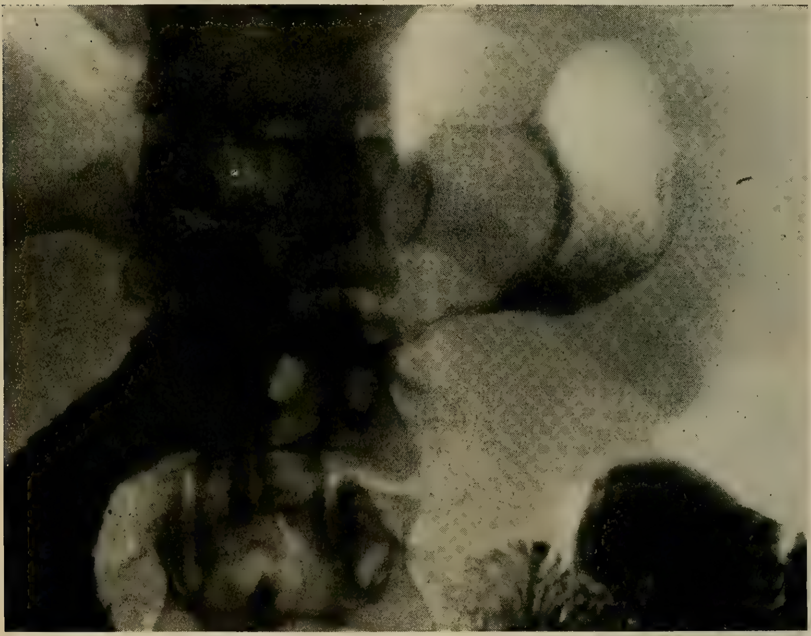

Fig. 81.—Roentgenogram of linitis plastica. On gastroscopic examination it was impossible to inflate the walls of the fundus with air. From this it may be deduced that most of the stomach was heavily infiltrated. This, of course, fits in well with the diagnosis of linitis plastica. (Courtesy of Dr. Paul Zackheim.)

defect on roentgenography, positive evidence elicited by gastroscopy and the persistence of occult blood in the stool and by biopsy of a sentinel lymph node, if present. Gastroscopy will apparently offer the most satisfactory method of establishing the diagnosis of the rare growths of the stomach when their presence has been manifested by roentgen procedures. In the presence of the characteristic findings mentioned the diagnosis of linitis plastica may be confirmed by the discovery of an accessible lymph node which on removal and section reveals the characteristic pathologic picture of carcinoma of this type.

TREATMENT

The diminished capacity of the stomach makes it necessary to feed small amounts of highly nutritious foods, such as milk, cream, malted milk, eggnog, sugar solutions, cream soups, ice cream, custards, fine cereals, puddings, finely cut portions of meat, fish, fowl, eggs, butter and puréed vegetables, at two hour intervals.

I know of no drugs except sedatives that will offer symptomatic relief. Despite a negative serologic reaction and the absence of other signs of syphilitic involvement, I believe that each patient for whom no biopsy is available is entitled to antisyphilitic therapy in the form of adequate doses of bismuth preparations and iodides. Radiation therapy has been of no avail. I have attempted to maintain nutrition in persons with this disease by the use of the duodenal tube. The necessity of its continued use and the inconvenience limit its application. The early recognition of linitis plastica and surgical resection constitute the most intelligent treatment.

PROGNOSIS

The disease may extend over a long period, the average duration, according to Lyle, being twenty-four months, but ultimately ends in death.

With the recent improvements in preoperative and postoperative care it has become possible to perform extensive gastric resection. For this as for all types of gastric carcinoma it is the sincere hope that one's suspicion of its presence may warrant early diagnosis and surgical interference to accomplish a satisfactory result.

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CHAPTER XVI

DUODENAL ILEUS AND STASIS

INTRODUCTION

Duodenal ileus and duodenal stasis frequently occur together, but do not represent a disease entity in the ordinary sense. They represent a syndrome due to a variety of causes, some of which are little understood. Clinical symptoms may be absent, vague or pronounced, and the results of treatment may be fruitless or brilliant.

DEFINITION

The term ileus implies obstruction to the passage of the intestinal contents, without designating whether the cause of the obstruction is functional or due to some definite organic condition. Clinically a diagnosis of duodenal ileus is usually employed to describe a partial obstruction of the distal part of the duodenum accompanied by varying degrees of dilatation and stasis. The condition is often of indeterminate origin, but it may be associated with some mechanical disturbance of function of the terminal portion of the duodenum. Duodenal ileus may be classified as functional or organic, congenital or acquired, acute or chronic and symptomatic or asymptomatic. However, the practical clinical problem of classification is simply the decision as to whether duodenal stasis with or without duodenal dilatation is purely a disturbance in function or whether it is caused mechanically by organic obstruction.

The incidence of duodenal ileus and stasis presenting a syndrome which merits a primary diagnosis is difficult to ascertain. The diagnosis is of only secondary importance when causative lesions are demonstrated to be exerting extrinsic pressure or intrinsic obstruction, and it is then frequently made. A primary diagnosis of chronic duodenal ileus has been recorded only three times by me in private and clinical practice, and in each instance no anatomic confirmation was possible. In 1928 Jewett[6] recorded 15 cases out of 30,000 general hospital admissions, a frequency of 0.05 per cent. The diagnosis of duodenal ileus has been listed 34 times in the files of the Stanford University Medical School department of radiology in a total of 11,385 gastrointestinal *x*-ray examinations, an incidence of 0.3 per cent. In each of 8 cases with such a diagnosis in which surgical exploration was done, an organic cause for the obstruction was found. Fishbaugh's[4] *x*-ray incidence was only 0.2 per cent in 5,000 cases. In Ophüls'[7] report of 3,000 autopsies not a single case of dilatation of the duodenum was noted, but Ratkóczi[8] found 29 cases in 4,500 autopsies, or 0.6 per cent. On the other hand, Wilkie[10] in 1927 reported 75 cases of chronic duodenal ileus, in a number of which the condition was apparently functional in origin, and just prior to this Halpert[5] reported his anatomic studies on arteriomesenteric occlusion of the duodenum, showing that clinically idiopathic chronic duodenal ileus can be due to mechanical pressure exerted by the mesentery. Actually it would seem that a primary clinical diagnosis of chronic duodenal ileus is rarely tenable and rarely substantiated.

ETIOLOGY

Etiologically, duodenal ileus can be divided into two types: (1) the idiopathic, commonly assumed to be functional in origin because no definite cause has been demonstrated clinically, and (2) the type for which there is an obvious organic cause. The first type may be divided into four subdivisions: (*a*) congenital dilatation or megaduodenum, (*b*) moderate dilatation associated with but not due to organic lesions, (*c*) chronic duodenal ileus of unknown genesis and (*d*) dilatation which may be due to vitamin B deficiency.

Megaduodenum congenitum is a relatively uncommon form usually observed in children. Hypertrophy of the duodenal musculature is rarely present. The cause is unknown, but may be some form of neuromuscular derangement similar to that thought to be the basic cause of Hirschsprung's disease. It has been reported also in adults. Dilatation of the duodenum with stasis has been observed to accompany duodenal ulcer and cholecystitis and may follow operations. The enlargement of the duodenum is slight as a rule and often asymptomatic. It is apparently due to a reflex disturbance of innervation, which is frequently temporary. Chronic duodenal ileus, with or without symptoms, as an isolated roentgenologic finding has been explained in a number of ways, none of which is completely satisfactory. Anatomic abnormalities are often assumed to be important. Chief of these is the presence of arteriomesenteric occlusion at the caudal end of the duodenum, frequently diagnosed but rarely satisfactorily demonstrated. In a few cases it has been shown to be due to arteriomesocolic occlusion associated with mobile colon. If the dilatation and stasis were commonly secondary to occlusion due to anatomic abnormalities, this would imply that a pronounced obstruction to the lumen is present, but the facts do not bear out this hypothesis.

However, the high incidence of disturbed duodenal function with dilatation, stasis and reverse peristalsis in the asthenic type of person with pronounced visceroptosis strongly suggests that duodenal ileus is merely one manifestation of a constitutional inferiority which commonly centers in the digestive tract. As such patients may have gastric atony and retention and a derangement of normal colonic activity resulting in stasis and constipation, it would seem reasonable to assume that disturbances of motility throughout the digestive tract have a common etiologic basis, apparently lack of coördination of the functions of the autonomic nervous system. That megaduodenum in adults, like megacolon, may be a manifestation of thiamin deficiency deserves careful consideration, as does the possibility of a similar relation of duodenal dilatation and stasis to colonic atony and stasis, which has recently been shown to be benefited by the administration of vitamin B_1.[2] No series of case studies is available as yet to substantiate the theory that functional duodenal ileus may, in some instances at least, be due to a vitamin deficiency, but duodenal ileus and certain forms of colitis show physiologic similarity.

The organic causes of secondary forms of duodenal ileus and stasis may be apparent from the clinical findings alone, but frequently a diagnosis of only duodenal obstruction and dilatation is made clinically, and the primary organic cause is found in the operating room or at the autopsy table. The causes may be: (1) congenital abnormalities, (2) constitutional defects, (3) cicatricial tissue due to ulcers, (4) adhesions, (5) external pressure, (6) foreign bodies, (7) granuloma, (8) primary tumors or (9) extrinsic malignant disease.

(1) Congenital abnormalities are intrinsic or extrinsic and may cause symptoms in adult life as well as in infancy. With congenital intrinsic obstruction there may be stenosis or atresia due to arrested or incomplete development of the intestine in its solid stage. Stenosis may occur also at the level of the ampulla of Vater, owing to improper fusion of the foregut with the hindgut. These forms of duodenal obstruction are rare but well recognized. Extrinsic compression by adhesions or bands of fibrous tissue of congenital origin has been reported not only in infants but in adults and is also rare. (2) Constitutional defects leading to arteriomesenteric occlusion of the duodenum or occlusion caused by distortion from a mobile colon may occur as already described. (3) Constriction of the lumen of the duodenum due to scar tissue from ulcers usually occurs in the first portion of the duodenum and causes only gastric dilatation and stasis. Occasionally ulceration takes place so far beyond the pylorus that the proximal part of the duodenum as well as the stomach is dilated. This is more likely when ulceration is associated with diverticulitis. However, duodenal ileus is not uncommon secondary to ulceration and scar tissue in the jejunum at the stoma of a gastrojejunostomy. (4) Adhesions from a pericholecystitis, a perforated peptic ulcer or any type of upper abdominal operation could cause constriction of the duodenum leading to partial obstruction and stasis, but there are few verified cases to prove such a cause of duodenal ileus. (5) External pressure on the duodenum by another viscus or by a tumor mass may interfere with normal duodenal function. It is conceivable that a distended gallbladder may act in this way, but this is unlikely in the absence of adhesions between the gallbladder and the duodenum. An enlarged liver may compress the duodenum so as to lead to duodenal ileus. I have a case under observation in which this is apparently true. Enlarged mesenteric lymph nodes may compress the fourth portion of the duodenum or an abdominal aneurysm the second portion. Enlargement of the head of the pancreas, which is commonly due to carcinoma but may be due to chronic pancreatitis, is a well recognized and not infrequent cause of duodenal ileus secondary to organic obstruction. Cancer of the head of the pancreas was the cause of obstruction in 43 per cent of Rivers and Thiessen's[9] series. (6) Foreign bodies obstructing the duodenum are rare. A large gallstone may erode into the duodenum, blocking its passage. Hair balls and parasites, such as tapeworm and roundworm, have been reported as causing duodenal obstruction. (7) Tuberculosis, syphilis and Hodgkin's disease are uncommon causes of duodenal obstruction. They may act through direct invasion or through compression of the terminal portion of the duodenum by involved glands. (8) Primary tumors of the duodenum are rare, but commonly cause obstruction. Duodenal polyps may block the lumen, as described in case 2 (*vide infra*), in which practically complete obstruction occurred in the lower part of the duodenum. A similar lesion due to a large angioma[1] has been reported. Carcinoma of the duodenum, particularly at the ampulla of Vater, is relatively infrequent and nearly always leads to obstruction. (9) Extrinsic malignant disease invading the duodenum usually arises from the pancreas, the gallbladder and bile ducts or the retroperitoneal region or may be due to metastases from any source.

SYMPTOMATOLOGY

It is my belief that the symptoms so often described as characteristic of chronic duodenal ileus are in no way specific for this condition and that their enumeration is important only to point out that they may accompany duodenal stasis and dilatation. Consequently, their presence in the absence of other causative factors may justly lead to a consideration of whether they are primarily due to duodenal ileus.

The symptoms which are due to dilatation of the duodenum from organic obstruction and which are often attributed to duodenal ileus are similar to those of pyloric obstruction, as described in the second case report. They are: epigastric fulness with gaseous distention and flatulence; pain, which may be severe and colicky and is likely to be aggravated by the ingestion of food; attacks of nausea and protracted vomiting; headache, which is frequently said to be a characteristic complaint, and often great prostration, particularly when the vomitus is copious and contains large amounts of bile. These manifestations frequently appear in recurring attacks, which may date from childhood and are likely to be precipitated by nervousness, anxiety or fatigue. Occasionally rapid relief is obtained by having the patient lie on one side, lie prone or assume the knee-chest position. Although these symptoms are clearcut and readily recognized, they may develop with almost any serious abdominal disease, such as cholecystitis, peptic ulcer or gastric cancer, and they often appear with such little understood conditions as migraine, abdominal allergy and visceroptosis. Intermittently symptoms may disappear entirely or they may be extremely mild. Also moderate degrees of duodenal dilatation and stasis with reverse peristalsis are demonstrated roentgenologically in patients who are entirely free from gastrointestinal complaint.

No characteristic physical findings suggest the presence of duodenal ileus, unless one considers the asthenic habitus of the visceroptotic person, who shows dilatation of the duodenum with stasis more frequently than other biologic types. Physical evidence of a dilated stomach with succussion sounds indicates gastric retention, but this may be accompanied by duodenal retention when obstruction is present in the duodenum. Varying degrees of upper abdominal tenderness and muscle spasm may be encountered.

ROENTGENOLOGIC FINDINGS

Although the symptomatic and physical findings are of little or no positive value alone, the roentgenologic manifestations deserve careful consideration. Those patients with *x*-ray findings indicative of duodenal ileus may be divided into three general groups (Fig. 82). For the first group the *x*-ray changes may be designated as indefinite or doubtful. Slight to moderate dilatation and stasis are observed, and often the roentgenologist calls attention to reverse peristalsis in the duodenum, commonly described as a churning or writhing of the intestinal contents back and forth. These findings are likely to be inconstant on the same day or absent on a second day's examination and frequently disappear when the patient is lying down, particularly if the prone position is assumed. They are usually unassociated with any complaint during the period of observation and are most often seen in visceroptotic persons who either are free from complaints or have vague complaints and are often styled "psychoneurotic." Of the Stanford University Hospital x-ray series, the majority of patients with an x-ray diagnosis of chronic duodenal ileus, 18, representing 0.16 per cent of the total number, fell into this group. The second group is composed of patients with constant and pronounced duodenal dilatation and stasis for whom there was no positive evidence of any causative lesion on x-ray examination and who did not come to operation or autopsy. My case 1 is typical of this group. Most of the patients had complaints that might be attributed to their duodenal ileus and might be classified as properly belonging under the etiologic heading of arteriomesenteric obstruction. However, there was no patient in this whole series who came to operation for whom some other definite cause of the obstruction was not demonstrable. Seven patients of the Stanford series, or 0.06 per cent, were in this second group. In the third group of patients, duodenal ileus was demonstrated to be due to some definite organic disease, such as adhesions, ulcer or tumor. My case 2 is an excellent example of this group, the cause being established as benign polyposis. Only 9 patients, or 0.08 per cent, of the Stanford series were in this last group.

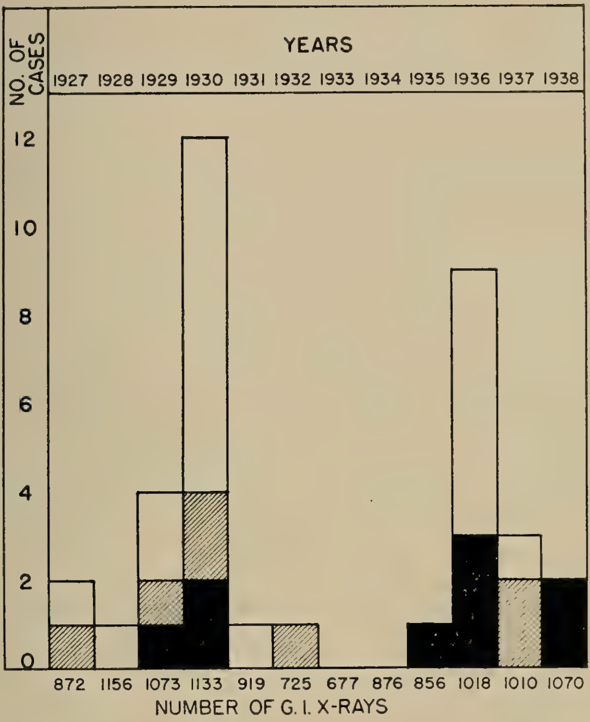

FIG. 82.—Graphic representation of the incidence of the x-ray diagnosis of duodenal ileus, shown by years, among 11,385 gastrointestinal examinations made during the twelve years from 1927 to 1938. The white blocks indicate clinically doubtful lesions (18 cases); the cross-hatched blocks, disease of unknown origin (7 cases), and the black blocks, lesions due to organic causes (9 cases). The marked variations in incidence may be explained by the varying degrees of enthusiasm of different roentgenologists for the diagnosis of chronic duodenal ileus.

A detailed description of the x-ray findings and the procedures to demonstrate these findings has been given by Feldman,[3] who suggested that mild duodenal ileus may be frequently encountered if the technical skill of the radiologist is high. However, review of his work makes evident the great difficulty of differentiating clearly where marked physiologic variations end and definite pathologic manifestations begin.

DIAGNOSIS

The diagnosis of duodenal ileus and stasis may be made from (1) the clinical examination, (2) the x-ray observations and (3) the operative findings. A history of recurrent attacks of upper abdominal distress and pain with nausea and vomiting accompanied by severe headache and prostration should arouse a suspicion of duodenal obstruction if other, more frequently encountered causes of these symptoms are absent. A history of the recent development and progression of these symptoms with evidence of gastric dilatation on physical examination indicates the probable presence of either pyloric obstruction or gastroduodenal ileus. All the evidence obtained from clinical examination is of minor importance when compared to the roentgenologist's observations, although these may be a cause for error in diagnosis.

The conservative roentgenologist pays little attention to minor degrees of dilatation, stasis and churning of the intestinal contents, although many of the diagnoses of chronic duodenal ileus in the Stanford x-ray series were based on such evidence alone (Fig. 82). It is noteworthy that in half of the cases in the group the diagnosis was made by one radiologist during the twelve-year period and in eight by another from 1927 to 1930. Another experienced member of the staff made the diagnosis in only 5 cases during the whole twelve-year period, and in 3 of these organic obstruction of the duodenum was subsequently demonstrated. Constant duodenal dilatation and stasis were encountered in 16 instances, or 0.14 per cent of the cases, and required an explanation of the cause. Definite evidence of an obstructing lesion was shown to be present in 9 of these cases. Of the remaining 7 cases carrying a roentgenologic diagnosis of duodenal ileus and stasis, in some there were no symptoms referable to the upper part of the digestive tract, and in others multiple abdominal operations had been done, so that bowel adhesions may well have caused some of the complaints. In 2 recently observed cases of gastroduodenal ulcer with obstruction in the second portion of the duodenum, due in one to scarring from ulcer and in the other to tumor, x-ray examination revealed no duodenal dilatation or stasis.

The frequency of a radiologic diagnosis depends primarily on the observer's interpretation of the significance of reverse peristalsis in the duodenal loop with transient stasis and at times some dilatation. This is well shown by the data presented in figure 82. Serial examinations covering one to several hours may be necessary before a final opinion can be voiced as to the degree of abnormality. Enough cases of moderate duodenal ileus and stasis without obvious organic cause exist so that the roentgenologist's diagnosis cannot be overlooked.

The final word as to diagnosis rests with the surgeon or in a few instances with the pathologist. The majority of patients operated on show evidence of a definite lesion causing the obstruction, and usually a laparotomy is required to identify the lesion. When the lesion is said to be due to the drag of the mesentery across the third portion of the duodenum, abdominal adhesions, bands or some other definite constricting lesion usually is seen at operation, but in some instances such evidence of obstruction is lacking. The results of anastomosing operations are almost universally bad in this second group. Although only 8 of the 34 patients in the Stanford series came to operation, all showed organic obstruction not explainable by the arteriomesenteric occlusion theory. One obstruction was due to tuberculous enteritis.

TREATMENT

If there is sufficient clinical and roentgenologic evidence to warrant a diagnosis of duodenal ileus and stasis, medical treatment should be given a thorough trial except in cases of obvious organic obstruction, in which operation is definitely indicated. Rest in bed for one or more weeks or until symptoms are relieved is desirable. Changes in posture, such as elevating the foot of the bed 12 inches, turning on one side or the other for an hour after meals, assuming a prone or a knee-chest position or sitting well forward in bed, should be tried. Occasionally upper abdominal distress will be relieved by one of these procedures. A bland diet is indicated, and for under-nourished patients this should be high in calories. Six relatively small feedings a day will be better tolerated than the usual three large meals. Particular attention must be paid to the patient's dietary idiosyncrasies, as many patients attribute their digestive symptoms to certain articles of food which are in reality harmless for them. Moist or dry heat applied to the abdomen will promote temporary comfort, and an abdominal support may diminish the distress of some of the ambulatory patients.

No drug can be called specific unless it is ultimately shown that duodenal dilatation, in some instances at least, is associated with a deficiency of vitamin B_1 or of some other member of the vitamin B complex. Thiamin chloride may be tried in a dose of 3 to 6 mg. daily by mouth, or may be administered hypodermically in a dose of 33.3 mg. every other day for pronounced involvement. Acetylcholine has been reported to give good clinical results in doses of 100 mg. daily. Symptomatically a mild sedative, such as bromide or phenobarbital, is often indicated for nervousness, and 10 grains of aspirin alone or in combination with phenacetin and caffeine, to relieve the headache. Codeine, 1 grain, may be necessary for severe aching or pain. Gaseous distress is common and may be alleviated with a mixture of equal parts of bismuth subcarbonate and sodium bicarbonate or with hot peppermint tea. Mineral oil, petrolagar and the vegetable mucinoids in doses appropriate to the patient are often necessary for constipation.

Organic obstruction of the duodenum must be dealt with surgically whenever there is hope of a cure or at least of temporary relief of symptoms. Extrinsic causes of stasis, such as adhesions, mesocolic bands and large lymph glands, and intrinsic causes, such as foreign bodies and benign tumors, are usually readily removed and the stasis relieved. If the normal contour of the duodenum cannot be restored in this way, or if the narrowing, of the lumen is due to scar tissue, chronic inflammation or annular pancreas, a duodenojejunostomy is indicated and usually gives excellent results. Satisfactory results have also been reported for this procedure in some cases of duodenal ileus and stasis thought to be due to arteriomesenteric occlusion, but the less definite the organic cause of the obstruction, the poorer the results of operative intervention. Patients with psychoneurotic tendencies and manifestations of functional gastrointestinal disorders will rarely be relieved by operative procedures.

Illustrative Cases

CASE 1.—Mrs. L. M., a housewife, aged fifty-six years, first came under observation when she entered the hospital on May 8, 1930, complaining of stomach trouble. She had been well except for recurrent attacks of hay fever until she contracted influenza fourteen months previously. Since then she had suffered from loss of appetite, gas on the stomach, sour eructations, nausea and frequent vomiting right after eating, dizziness, ringing in the ears and constipation, and had lost 50 pounds. An appendectomy was performed two months after the onset of her illness, without any relie. Various forms of diet and laxatives had failed to improve her symptoms. Physical fexamination at the time of hospital entry, including pelvic examination and proctoscopic examination of the rectum, failed to reveal any abnormalities except moderate under-nutrition and slight abdominal muscle spasm in the epigastric region. A urinalysis, examination of two stool specimens, a blood count, a blood Wassermann test and a histamine fractional gastric analysis failed to reveal any abnormalities. A gastrointestinal x-ray study showed the stomach normal, but the second and third portions of the duodenum were markedly dilated (Fig. 83) and showed marked retroperistalsis. Two hours later the same unusual duodenal findings were evident. Six hours later some residue was still present in the duodenum, while the stomach was empty. Examination of the rest of the small bowel and of the large bowel, including a study of the colon with a barium enema, gave negative results. The gallbladder was visualized normally. A second x-ray examination of the duodenum eleven days after the first showed the same picture.

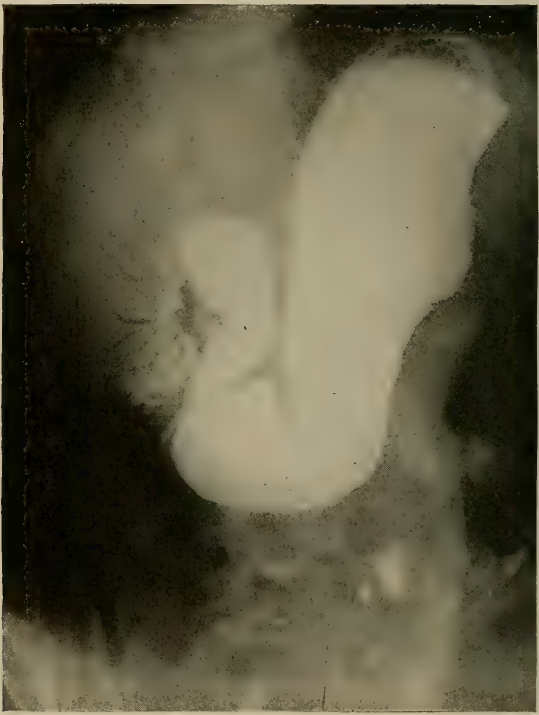

FIG. 83.—Roentgenogram made in case 1, showing duodenal stasis and dilatation of unknown origin.

Therapy during hospitalization consisted of frequent feeding of small amounts of food, with giving of belladonna after meals and of bromides at bedtime. The foot of the bed was kept elevated on blocks a foot high. The patient coöperated poorly and displayed definite psychoneurotic tendencies. A surgical consultant believed that duodenojejunostomy was not indicated. She was dismissed unimproved on May 22, 1930, with a clinical diagnosis of constipation and psychoneurosis. She was not seen again until November 1937, but in January 1937 her daughter stated that she had been free of symptoms since a home scene following her return from the hospital, during which she was told there was nothing wrong with her except her mental attitude toward life. On November 29, 1937, she complained of constipation and low abdominal distress, but refused further x-ray studies.

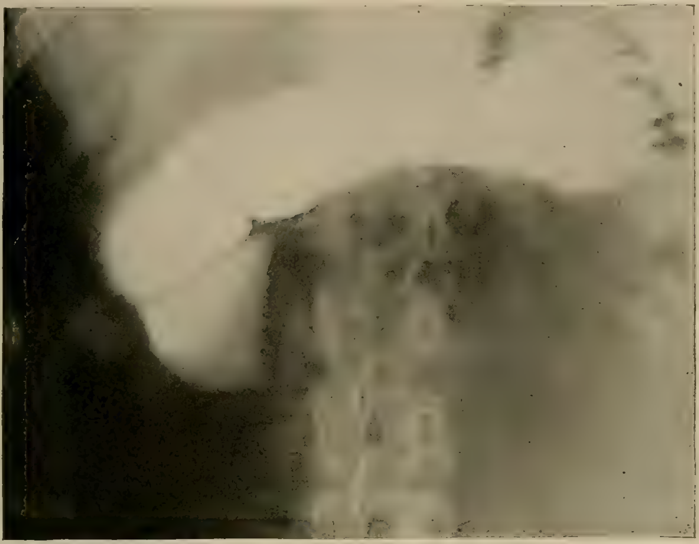

FIG. 84.—Roentgenogram made in case 2, showing obstruction of the distal part of the duodenum, with proximal stasis and dilatation. The obstruction was due to benign polyps.

CASE 2 (*Duodenal Stasis and Dilatation Due to Duodenal Polyps*).—Mrs. B. T., a housewife, aged sixty-two years, entered the hospital on Aug. 29, 1935, complaining of vomiting. During the past nine months there had been recurrent gastric distress and vomiting fifteen minutes to two hours after meals, loss of appetite and progressive weakness. From an original weight of 200 pounds she had gone down to her present weight of 100 pounds and become so feeble she could not get out of bed. The physical examination gave essentially negative results, except for pallor, emaciation, loss of skin turgor and an indefinite upper abdominal mass thought to be a loop of bowel, which was found by some examiners and not by others. The urine was normal. The blood Wassermann reaction was negative. The stools showed a strongly positive reaction for occult blood. Repeated blood counts showed a marked normocytic anemia, with a color index of about 1, and a normal leukocyte count. The blood urea content was 51 mg. per hundred cubic centimeters. The blood chloride level was 280.5 mg. A histamine gastric test meal revealed only a trace of free acid. At the gastrointestinal x-ray examination, the stomach was normal in outline, but the duodenum was dilated, and there was a marked retention of barium in both the stomach and the duodenum. There appeared to be a partial obstruction in the region of the fourth portion of the duodenum, thought to be due to an extrinsic tumor mass. Two further x-ray studies revealed essentially the same picture (Fig. 84).

On Sept. 28, 1935, the patient was operated on for obstruction of the small bowel. The upper part of the jejunum was found to be greatly dilated, and there was an intussusception of the distal part of the duodenum into it. In the third portion of the duodenum was a large sessile polyp. The intussusception was reduced and the polyp resected. She made a slow but satisfactory recovery, except that a moderate anemia persisted up to the time of hospital dismissal, six weeks after operation. She is known to be well three and one-half years later and has gained back the 100 pounds she lost.

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PART III

The Liver, Gallbladder and Pancreas

CHAPTER XVII

PHYSIOLOGY OF THE LIVER, BILE AND GALLBLADDER

LIVER

Physiologic Anatomy.—The liver is the largest gland in the mammalian organism; it weighs 1.4 to 1.6 Kg. in men and 1.2 to 1.4 Kg. in women. This great gland, besides secreting bile, is concerned in almost all the metabolic activities of the body.

Structure of the Liver.[20]—The structure of the liver is rather simple when it is once comprehended. It is composed of anatomic-functional units called lobules. The lobule is a five to seven sided polygonal prism consisting of a central vein, blood sinusoids, cords of hepatic cells which surround a bile capillary and Kupffer or retriculoendothelial cells, which line the sinusoids. Interspersed among the lobules at their periphery are found clumps of connective tissue which give off strands that separate more or less one lobule from another and which contain a branch of the hepatic artery, a branch of the portal vein, a small bile duct, a lymphatic duct or ducts and nerves (Fig. 85). This connective tissue, known as Glisson's capsule, or the periportal connective tissue, starts at the porta of the liver, where the portal vein, hepatic artery, hepatic bile ducts, lymphatic vessels and nerves enter, and extends into the liver along the branches of the ducts and vessels just mentioned. The branches of the hepatic vein or the sublobular veins which connect with the central vein of the lobules are surrounded with little connective tissue.

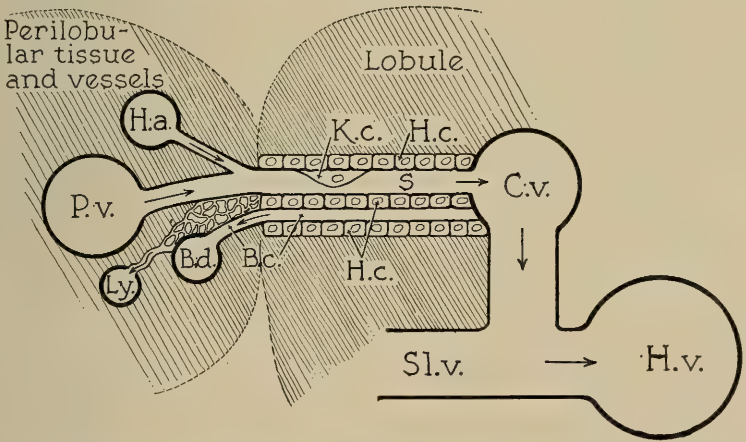

FIG. 85.—Diagram illustrating the circulation of fluids in the liver. *H.a.* designates hepatic artery; *P.v.*, portal vein; *S*, sinusoid; *C.v.*, central vein; *Sl.v.*, sublobular vein; *H.v.*, hepatic vein; *K.c.*, Kupffer cell; *H.c.*, hepatic cell or cord; *B.c.*, bile capillary; *B.d.*, bile duct; *Ly.*, lymphatic duct.

In the dog, about 80 per cent of the blood received by the liver enters by way of the portal vein and 20 per cent by the hepatic artery. These two streams of blood mix at the periphery of the lobules, enter the sinusoids and then the central vein and thence go to the branches of the hepatic veins. The hepatic cells are in contact with the endothelial lining of the sinusoids on one side and the bile capillaries on the other. There is no basement membrane. On the sinusoid side of the hepatic cells, substances leave the blood and enter the cells, to be returned later to the blood or to be secreted or excreted into the bile capillary. Lymph vessels have not been found among the cells in the lobules; they are found among the terminal branches of the portal veins and the bile ducts in the periportal connective tissue. Neither do the nerves, which come from the splanchnic nerves and vagi—chiefly the former—enter the lobules; yet, when the hepatic nerves are stimulated, an immediate decrease in the diameter of the sinusoids occurs.

Activities of the Liver.—The liver manifests many activities. Its importance cannot be appreciated until one views and comprehends its many essential and diverse activities. The formation and secretion of bile are relatively less vital and important than its numerous metabolic activities. The seriousness of jaundice and of hepatitis depend chiefly on the degree of impairment of the metabolic activities of the liver.

Considering the multifold activities of the liver, its large factor of safety, 80 per cent, and its remarkable regenerative capacity, one is not surprised that a completely adequate test of hepatic function is unavailable. All the functional tests are directed toward ascertaining the extent of impairment of certain single activities. Until we find out why a hepatectomized dog dies in from twelve to forty-eight hours, we shall be working more or less in the dark, so far as adequate tests of the vital function of the liver and the treatment of hepatic insufficiency are concerned. In fact, the liver is now the only organ in the body whose removal results in unexplained death.

The activities of the liver other than the secretion of bile will be discussed under general topics: (I) the storage of food substances, (II) the manufacture of food substances, (III) the manufacture of other substances, (IV) detoxication and (V) regulation of blood volume.

I. **The Storage of Food Substances:**

A. *Carbohydrate.*—The dextrose, levulose and galactose absorbed into the portal blood during digestion are converted into glycogen (glycogenesis) or animal starch, which is stored in the liver. Under ordinary feeding conditions the liver contains from 4 to 5 per cent of glycogen. During fasting the glycogen is hydrolyzed (glycogenolysis) into dextrose and the dextrose is released into the blood stream. Glycogenolysis is speeded up by nerve impulses passing to the liver *via* the splanchnic nerves, by administration of epinephrine or thyroxin, by anoxemia or acidosis, by a fall in blood sugar, by exercise, etc. Some authors believe the vagi inhibit glycogenolysis. When the splanchnic nerves are cut, glycogen tends to accumulate in the liver.[17] *In fasting the glycogen store is depleted in from twelve to twenty-four hours*; then sugar must be manufactured by the liver from sources other than glycogen.

B. *Protein.*—Protein is stored in the liver.[15] During a two day fast the liver of rats loses 20 per cent of its original protein; other organs only 4 per cent. In a more prolonged fast the liver may lose 40 per cent of its original protein, which is probably stored as liver protein and not as a special protein analogous to glycogen.

C. *Fat.*—On a well balanced diet the liver contains only from 3 to 5 per cent fat, of which 40 to 70 per cent is neutral fat and the remainder phospholipin. A diet rich in fat tends to increase the fat content of the liver. When the glycogen content of the liver decreases, the fat content usually increases.[15b] Thus, during fasting the liver fat increases, if fat is present in the fat depots. Under abnormal conditions the liver may contain as much as 50 per cent fat. The fat content of the liver is increased by chloroform, phosphorus and carbon tetrachloride poisoning, and the glycogen content is decreased. Alcohol speeds fat deposition in the liver. After the production of a fatty liver with high fat feeding, the addition of alcohol has been observed to produce cirrhosis of the liver.[4] In the presence of a deficiency of pancreatic juice, fat accumulates in the liver; this may be prevented by feeding pancreas or lecithin or choline. In diabetic dogs receiving only insulin a fatty liver develops; this can be prevented or reversed to normal with lecithin, a high meat diet or lipocaic, a hormone which is thought to be produced by the pancreas and to regulate fat metabolism in part.[2] A diet low in protein or choline produces a fatty liver. Casein, albumin and beef muscle (without the extractives), in the order mentioned, are the best proteins, for preventing and relieving fatty infiltration of the liver in the presence of a choline- or protein-deficient diet.[11]

D. The liver stores an "*anti-pernicious anemia factor.*"[23] It stores vitamins A and D and is rich in the vitamin B complex. The liver is thought to store iron and copper.[21,24]

II. **The Manufacture of Food Substances:**

A. *Carbohydrate.*—Dextrose is the sugar of choice of the body cells. Some levulose, but little if any galactose, can be utilized by the body cells. When levulose and galactose are absorbed, they are converted into glycogen by the liver; then the glycogen is converted into dextrose. Thus, it can be said that the liver manufactures dextrose from levulose and galactose. Galactose, when it enters the systemic circulation, acts like a foreign body and is excreted in the urine. So in cases of hepatic disease galactose is used as an indicator of liver function. Lactic acid is converted to glycogen by the liver. So the lactic acid that gets into the circulation during and after exercise is converted into glycogen and finds its way back to the muscle as sugar; this has been called the Cori cycle.

B. The liver can make dextrose from certain of the aminoacids. Casein contains about 48 per cent of sugar-forming aminoacids; meat about 58 per cent, and certain vegetable proteins even more.

C. It is believed that the liver can make destrose from the glycerin portion of the fat molecule. Some authors believe that sugar can be made from fatty acids; this has not been established. The formation of sugar from aminoacids or protein and fat is called *gluconeogenesis.* During fasting and in the presence of diabetes mellitus dextrose is formed gluconeogenetically. *It is very evident, then, that the liver plays an essential role in the maintenance of the blood sugar level.*[3] This is why the blood sugar falls after hepatectomy or in the presence of severe hepatic disorders. This is not a vital function apparently, since a hepatectomized animal will die with the blood laden with dextrose given intravenously.

D. There is some evidence which indicates that the liver may make fat from dextrose or protein and glycerin.

E. The liver synthesizes the nonessential aminoacids.

F. The liver makes various organic acids, which may be oxidized to produce heat or used for synthesis of body substances.

G. The liver desaturates fatty acids, which renders them more reactive for purposes of building complex lipids.

H. The liver makes vitamin A from carotene, the yellow pigment in plants.

I. The liver makes ketone bodies, acetone, acetoacetic acid and beta-oxybutyric acid, and one theory regards ketone bodies as food.

III. **The Manufacture of Other Substances, Some of Which Are and Others or All of Which May Be, Essential for Body Economy:**

A. The embryo, liver and spleen manufacture red blood cells, and perhaps in certain emergencies the adult liver may revert to this embryonic function. There is some equivocal evidence indicating that the liver gives off a hormone that depresses erythropoiesis as well as one that stimulates the process.[8]

B. Blood fibrinogen and all the blood proteins are in part made in the liver. Heparin, or antiprothrombin, is made in the liver. The prothrombin in the blood is frequently decreased in the presence of hepatic disorders, which may or may not be due directly to hepatic insufficiency. Recently a substance has been extracted from the liver that promotes the coagulation of the blood and is reported to be of value in the presence of a hemorrhagic tendency.[14] In the presence of hepatic insufficiency blood proteins are not manufactured at a normal rate.

C. The liver makes ketone bodies. Dextrose prevents or retards the formation of these substances during fasting or in the presence of diabetes when insulin is present.

D. The liver makes the bile salts. The cholic acid molecule is closely related to cholesterol and all the sterols in the body, such as the hormones produced by the gonads and the adrenal cortex. Because cholic acid is conjugated with taurine, which comes from the aminoacid cystine, the liver is concerned in sulfur metabolism. Whether the manufacture of cholic acid serves the body in other ways than in the process of digestion and absorption of fats, sterols and vitamins A, D, E and K is uncertain.

E. Whether the liver makes cholesterol is uncertain, but it is certainly concerned in cholesterol metabolism, since in hepatic disease the values for blood cholesterol, free and esterified, are modified.

F. The liver makes urea from the ammonia resulting from the deamination of proteins. Blood urea falls in the hepatectomized animal, even after excision of the kidneys.

G. Some uric acid is made in the liver; uric acid may also be destroyed in the liver. The importance of the liver in uric acid metabolism in man is uncertain.

H. The liver forms some bile pigment or bilirubin. The amount of bilirubin formed intrahepatically and extrahepatically is unknown. The urobilin and urobilinogen absorbed from the intestine may be changed in part to bilirubin by the liver. The unchanged portion may be eliminated in the bile and urine.

I. The liver produces histamine in anaphylactic shock.

J. The liver probably produces antibodies.

K. Next to skeletal muscle ranks the liver as an important source of body heat.

L. The liver may produce glycuronic acid for the manufacture of mucin and other glycuronic acid–containing substances in the body.

M. The liver may produce the enzyme phosphatase, which splits glycerin esters of phosphoric acid and is thought to play a role in phosphorus metabolism. Much phosphatase is present in bile, and the marked elevation of phosphatase in the blood serum in obstructive jaundice is thought to indicate that phosphatase is eliminated in the bile. But when the hepatic duct draining one lobe of the liver is tied, serum phosphatase increases although bilirubinemia does not occur. This indicates that phosphatase is produced by the hepatic cells.[10]

N. There is some evidence indicating that the liver may remove any enzyme that might be absorbed into the portal blood during digestion. In the presence of hepatic insufficiency the olive oil–splitting lipase in the blood tends to be increased.[5]

IV. **Detoxication:**

A. The liver detoxifies certain substances by conjugation or by oxidation, reduction, methylation and acetylation. For example, indole is coupled with sulfuric acid to give indoxyl sulfate; phenol, benzoic acid, menthol and sex hormones in certain instances are coupled with glycuronic acid and eliminated in the urine as glycuronides; or glycine coupled with benzoic acid yields hippuric acid, a reaction which is utilized as an indicator of liver function. Sulfanilamide is partly acetylated by man and so treated appears in the urine. For other examples, a textbook of biochemistry should be consulted.

B. The liver serves also to eliminate certain heavy metals such as mercury, as well as certain drugs and bacteria from the body, by excreting them in the bile. Salyrgan, sulfanilamide, arsenic, cinchophen and salicylic acid are examples of drugs eliminated in the bile.

C. The liver assists in detoxication also by taking up and temporarily storing certain poisons. One example is the storage of strychnine by the liver of the chicken. The dog's liver can destroy strychnine; the rabbit's liver, atropine. A wide species difference occurs in regard to the destruction and storage of drugs by the liver.

D. The reticuloendothelial cells of the liver remove bacteria, foreign proteins, acacia, dyes, etc., from the blood stream.

A good example of an unknown type of detoxicatory activity of the liver is observed in Eck fistula dogs. (An Eck fistula is formed by anastomosis of the portal vein to the vena cava, followed by ligation of the portal vein at the hilus of the liver, an operation that shunts the portal blood into the systemic circulation.) These dogs manifest evidences of chronic hepatic insufficiency, and *when fed a large meal of only meat, they show symptoms of "meat intoxication" and may die.* Severe attacks are relieved by provoking emesis by giving an enema and injecting dextrose intravenously. Such animals do much better on a high carbohydrate diet with milk; also when a source of glycuronic acid, chondroitin, is fed. They rarely menstruate (or manifest estrus), and have never borne young.

When the liver has been injured with such a poison as chloroform, the regenerated cells are more resistant to chloroform intoxication.[16]

A liver well filled with glycogen and protein is said to suffer less from chloroform and phosphorus poisoning. An injection of dextrose may improve the coagulability of the blood in jaundice. Ascites is more likely to occur in cirrhosis of the liver if a high protein diet is fed than if a high carbohydrate diet is fed. However, if the liver, aided by diet, does not maintain the blood proteins at a normal level, ascites is likely to occur because the filtrability of the blood increases. Calcium is said to protect the liver from carbon tetrachloride poisoning.

Whether the "peptic" ulcer of the duodenum or stomach that frequently occurs in dogs[12] when the liver or bile ducts are interfered with is due to the impairment of some detoxicatory or synthetic activity of the liver or to a decrease in bile flow has not been ascertained. The same is true of the meningoencephalitis that frequently occurs in Eck fistula dogs kept for months in a state of "mild meat intoxication." The answer to these questions may pertain to the cause of "peptic ulcer in man, of familial lenticular degeneration (Wilson's disease) and of pseudosclerosis of Westphal, diseases in which evidence of hepatic disorder is present.[6]

V. **Regulation of Blood Volume**:

The liver tends to prevent dilution of the blood after the drinking of water. The blood of Eck fistula dogs is diluted by the oral administration of a volume of water that causes no dilution in a normal animal.[7] In this connection it is claimed that the liver is important in maintaining the normal ionic equilibrium of the blood and that water absorbed into the portal circulation is retained better by the body than water introduced parenterally.

The liver, like the spleen, serves as a reservoir for erythrocytes and fluid and acts something like a "flood chamber" to prevent over-distention of the right side of the heart.[13]

The Relation of the Liver to the Endocrine Glands.—A. **Islets of Langerhans.**—The diabetic liver is practically glycogen free. The administration of insulin causes the diabetic liver to store glycogen. The explanation of this fact is that in the absence of insulin, regardless of hyperglycemia, the liver is over-producing dextrose through the mechanism of gluconeogenesis and that the insulin retards gluconeogenesis. In a normal animal the injection of insulin "drives" dextrose into the muscles and other tissues and decreases blood sugar, which stimulates glycogenolysis, and since gluconeogenesis is retarded, the liver is deprived of glycogen. According to these views, it is not rational to give insulin with dextrose to a patient with hepatic insufficiency with the idea of "forcing" the dextrose into the liver.[1]

B. **Hypophysis.**—The removal of the hypophysis in a diabetic animal (a Houssay dog) abolishes or markedly relieves the hyperglycemia and glycosuria. If an appropriate extract of the anterior lobe is injected into such an animal, hyperglycemia and glycosuria return. It is believed that the hypophysis produces a hormone which increases glycogenolysis and gluconeogenesis. In fact, prolonged daily injections of the anterior lobe extract will induce diabetes which persists for some time after cessation of the injections. An extract of the anterior lobe which causes ketosis, probably by acting on the liver, also can be made.

C. **Adrenal Glands.**—The cortex of the adrenal glands also is thought to increase gluconeogenesis; when these glands are removed from a diabetic animal the effect on hyperglycemia and glycosuria is analogous to that of hypophysectomy. Epinephrine causes hyperglycemia by increasing glycogenolysis.

D. **Thyroid.**—A low glycogen reserve exists in the liver in hyperthyroidism. According to the results of animal experiments, the administration of vitamin B decreases the glycogenolytic effect of desiccated thyroid.[9]

Effects of Extirpation of the Liver.—The effects of extirpation of the liver in the dog,[18] in which animal the effects are best known, will be briefly listed. Death results in from twelve to eighteen hours. Hypoglycemia occurs soon after the operation, and dextrose administration and preservation of body warmth may prolong life up to forty-eight hours. A rise in bilirubin occurs in the blood, which shows that bilirubin is made in part extrahepatically. The blood urea content falls almost to zero, and the uric acid level rises. (The dog excretes allantoin, which is made from uric acid by its liver.)

Total ligation of the arterial blood supply of the liver is reported to cause death; ligation of the hepatic artery near its origin is not fatal, owing to collateral circulation. Extensive necrosis of the liver is fatal not only because of relative hepatic insufficiency but because of absorption of the necrotic tissue.

Factor of Safety and Regeneration of Liver Cells.—Only 20 per cent of the normal liver may maintain its normal functions. The capacity of the liver to regenerate is remarkable.[19] When 70 per cent of the liver in rats and dogs is removed, 90 per cent regeneration will occur in a few weeks. Reduction of the portal blood supply, obstruction of a bile duct or cirrhosis of the liver prevents or retards regeneration. Regeneration can occur, however, in a liver in which cirrhosis is progressing because of the administration of carbon tetrachloride. The regenerated liver cells under certain conditions are known to be more resistant than the original ones to the poison which caused the necrosis.

Regeneration of liver tissue is more rapid when a high carbohydrate diet is given; it should be remembered that protein also is required for building protoplasm, and milk and eggs are complete foods in this regard. The regenerative process is said to be inhibited by a high fat diet.[22] Regeneration of the liver, of course, is known to occur in man.

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(For more numerous references the reader is referred to the chapter on Liver and Bile in the *Annual Review of Biochemistry*)

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BILE

Bile is the external secretion of the liver. It serves as a digestive secretion because of its bile salt and fluid content. It contains excretory products, of which bile pigment is an example, the liver being an excretory as well as an external and internal secretory organ.

The chief constituents of bile in addition to water are *a*, bile pigment, *b*, bile salts, *c*, cholesterol, *d*, fatty acids, *e*, phospholipin, *f*, a mucin-like substance and *g*, practically all the inorganic constituents of blood plasma, including carbon dioxide. The type of pigment and bile acid present is subject to species variation.

Physical Characteristics.—Bile varies in *color*, depending chiefly on the concentration and type of pigment present. Liver bile, owing to its pigment, is normally golden yellow or light orange brown in man. Gallbladder bile is darker. If biliverdin, or oxidized bilirubin, is present, the bile varies in color from green to black. The *specific gravity* varies from 1.008 for fistula bile to 1.050 for gallbladder bile. Liver bile has approximately the same *osmotic pressure* as blood (it depresses the freezing point about 0.56 to 0.61 C.); that is, bile is secreted isosmotically. Even gallbladder bile is isosmotic with blood. The *reaction* of liver bile is slightly alkaline (*p*H of 7.4) but becomes more alkaline (*p*H 8.0 to 8.6) on standing, owing to loss of carbon dioxide. Gallbladder bile is usually slightly acid (*p*H 5 to 6). The *viscosity* of bile varies widely; it does not depend so much on the total solid content as it does on the protein and lipid content.

Bile is a very complex secretion. Much has yet to be learned regarding its composition. With few exceptions, *e. g.*, those for cholic acid, sulfur and inorganic constituents, the methods of analysis are not quantitative.

Quantity of Bile Secreted.—The quantity of bile secreted by the human liver in the presence of fistula has varied from 500 to 1,000 cubic centimeters per day. Many data on the subject are of little value, since they have been obtained under all sorts of conditions, with and without the return of bile or bile salts, etc., to the intestine. Although some authors have said that from 1,000 to 1,500 cubic centimeters is too high an estimate, that value may be accurate for normal physiologic conditions. In the dog with a bile fistula, in which conditions may be controlled and the resistance offered by the rubber tubing draining the bile duct overcome by slight suction, the following quantitative data have been obtained: The volume output of bile in 7 dogs receiving no food and no bile ranged from 6 to 10 cubic centimeters per kilogram per day; that when a mixed diet was fed every six hours without the slow postcibal return of bile to the duodenum was 13 to 18 cubic centimeters per kilogram; that when the same diet was given with the return of bile to the duodenum was 24 to 27 cubic centimeters per kilogram per day. Thus, there is a basal endogenous output, which is doubled by the feeding of a meal containing considerable meat and almost redoubled by the return of the bile secreted.[9]

Water as usually ingested has no effect on volume output, but appetite has a marked effect. When food is consumed without relish, less bile is formed than when the same food is consumed with relish. Nausea and vomiting definitely decrease bile volume output, even when the meal is promptly reingested. If the daily caloric intake of a mixed diet is maintained constant, the quantity of bile secreted is somewhat greater on a six hour feeding schedule than on a twenty-four hour single feeding schedule. Feeding more frequently than every six hours has no effect on volume output. It has been maintained that a diurnal variation in bile secretion exists, but it does not exist when a meal is fed every six hours. If a meal is fed at 6 A.M., at 12 noon and at 6 P.M. and then none is given at midnight, of course less bile will be formed during the night than during the day.[9]

More bile is formed on a high protein diet, probably because more cholic acid is formed. One hundred grams of beef liver is about 25 per cent more potent than 100 Gm. of lean beef. Per gram of weight liver bile is more potent than any food, so far as volume output of bile is concerned. Of course, gallbladder bile is more potent than liver bile. Olive oil given with or without bile every six hours stimulates bile output for several meals and then no longer stimulates. Added to a mixed diet, it does not stimulate bile output, which may be due to a delay in gastric evacuation caused by the fat. Dextrose inhibits bile output unless bile is being absorbed from the intestine. When it is added in reasonable amounts to a mixed diet, it has no effect on bile output.

The Changes in Volume and Composition of Bile After a Mixed Meal.—The literature is not in agreement regarding the effect of a meal on the output of bile and its constituents. This is because the test conditions have not been adequately controlled or the methods quantitative. Unless the method is quantitative the relatively slight increase that occurs after a meal without the return of bile will be missed or declared insignificant.

The data shown in figure 86 are typical of the changes in the volume of bile, and the cholic acid, pigment and cholesterol output after the ingestion of a mixed meal, with and without bile entering the intestine. This is the response of a healthy dog, and there is no good reason to believe that the response of the human being should be any different.[17a]

Origin, Fate, Toxicity and Function of the Better Known Constituents of Bile.—The Bile Acids.—Chemically cholic acid is closely related to cholesterol, the sex hormones, the carcinogenic hydrocarbons and vitamins A and D and possibly K. For this reason and because the physician frequently uses bile salts therapeutically, the structural formulas of the most frequently mentioned bile acids will be given (Fig. 87).

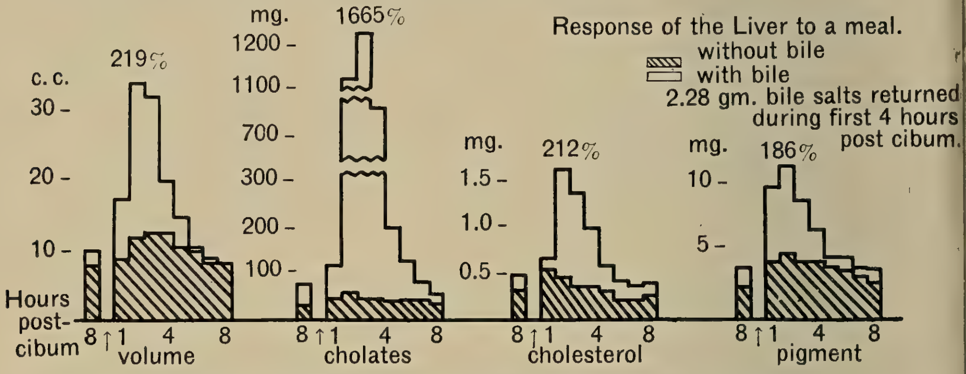

FIG. 86.—Chart showing the hourly output of bile (*volume*), cholates, cholesterol and pigment following a meal with and without the return of bile to the intestine.

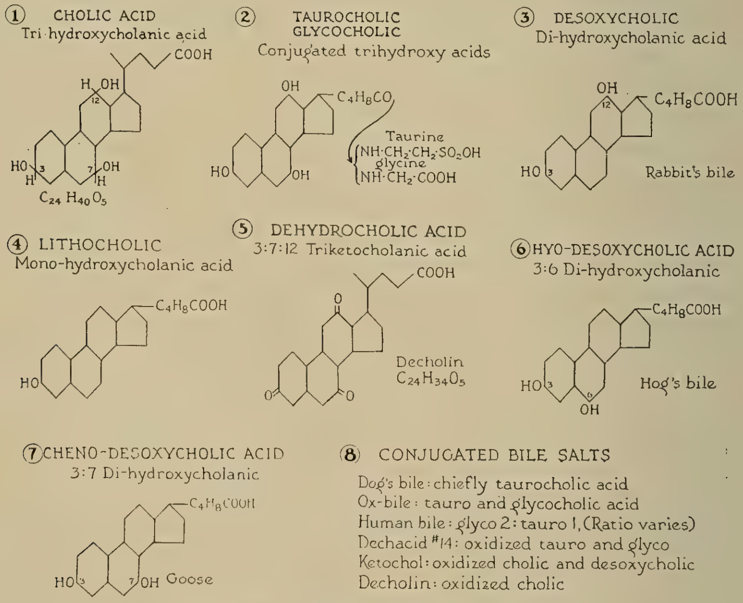

FIG. 87.—Structural formulas of the bile salts.

The bile acids are made by the liver. The evidence indicates that they are made from protein, not cholesterol.[21] In obstructive jaundice they may appear in the blood and urine in small amounts during the first week or two, and then the liver appears to cease their manufacture. Even after the obstruction is released, bile salts may not appear in the "bile" until after several days or two weeks. Hepatitis also decreases and may abolish their formation.[10]

The bile acids are chiefly eliminated in the bile as sodium salts. The conjugated unoxidized bile salts, *i. e.*, sodium taurocholate and glycocholate, are rapidly absorbed from the intestine. If 5 Gm. of bile salts is given orally, nearly all is absorbed and excreted in the bile in from six to twelve hours. This is referred to as the *enterohepatic circulation of bile salt.* During the enterohepatic circulation about 10 per cent of the cholic acid is lost. Just where it is lost is uncertain. The bile acids are either destroyed internally at a rate which balances their endogenous formation or eliminated in the feces.

The bile salts are toxic—in fact, they are the only known toxic constituents of bile. They are cytolytic. The oxidized bile salts—for example, sodium dehydrocholate (decholin sodium)—are considerably less toxic when ejected intravenously than the conjugated bile salts. For this reason sodium dehydrocholate is the bile salt of first choice for intravenous medication. Relatively little is known regarding the metabolism of the various bile salts used therapeutically.[17b]

The bile salts *function* as follows: 1. They aid in digestion and absorption. 2. They act on the liver to increase the output of bile. Pure bile salts under normal conditions do not increase the output of pigment, but may do so in the presence of hyperbilirubinemia. 3. Given orally or intravenously in pure form, they increase the total output of cholesterol in the bile. 4. By stimulating the formation of bile they act as a sort of laxative for the biliary passage. Although cholesterol is somewhat soluble in aqueous solutions of bile salts, it is more soluble in soaps (fatty acids). 5. By keeping the fatty acids in aqueous solution at the acid reaction of gallbladder bile they prevent the precipitation of cholesterol and fatty acids in the gallbladder. 6. They stimulate the motility of the intestine and colon, particularly when present in excessive amounts. Given intravenously they depress the tone of the musculature of the gallbladder, sphincter of Oddi and intestine.

The amount of bile salt contained in the bile varies widely. Probably the most reliable figure for the cholic acid content of "normal" human fistula bile with the subject on a mixed diet is 2 Gm. per hundred cubic centimeters of bile.[4] The figures found in the literature vary from 0.2 to 2 Gm. per hundred cubic centimeters for liver bile.

Bile Pigment.—The pigment in the bile comes chiefly from hemoglobin and represents the wastage of erythrocytes that has occurred extrahepatically or intrahepatically. Some may come from the hemoglobin of red muscle.

The first oxidation product of bilirubin is biliverdin, which may be found in the human gallbladder bile or *in static common duct bile.* When bilirubin is reduced urobilinogen results, and this on further reduction produces urobilin. This reduction is produced normally by putrefactive bacteria in the intestine or abnormally in the liver or biliary passages. Porphyrins, originating from hemoglobin, are produced in the intestine; they are thought to be present rarely in bile. (For a review of the recent literature see Ivy and Gray.[7])

Some bilirubin is always present in human serum. It varies in amount from 0.2 to 0.5 mg. per hundred cubic centimeters of blood. It is said to be present to a greater extent in asthenic than in sthenic persons. The bilirubin that is normally in the blood reacts differently from the bilirubin that has been acted on by the hepatic cells, in that the former has to be digested with alcohol before it gives Ehrlich's diazo reaction and the latter does not, or the former bilirubin acts "indirectly" with the diazo reagent and the latter "directly" without treatment with alcohol. The bilirubin which has been acted on by hepatic cells or by bile acids is more permeable to the capillaries than that which has not; this is why more bilirubin has to be in the blood to cause bilirubinuria and staining of the tissues in the presence of hemolytic jaundice (indirect reaction) than of obstructive jaundice (direct reaction).

Most of the bilirubin that enters the intestine is excreted in the feces. Yet, when bile is returned to the intestine of a dog with a biliary fistula, the output of bile pigment in the bile is increased on the average to about 33 per cent. This is referred to as *the enterohepatic circulation of bile pigment.* When pure bilirubin is put into the intestine, some authors say that it is partly absorbed, others that it is not. All agree that urobilinogen and urobilin are absorbed from the intestine. In fact, when urobilin is fed, some appears in the bile as urobilin. If the liver is injured or insufficient, urobilin and urobilinogen pass into the general circulation and appear in the urine. Traces of urobilinogen normally appear in the urine; but the presence of excessive amounts indicates that bile pigment is entering the intestine but the liver is injured to such an extent that the urobilinogen is not being normally removed from the portal blood. If there is excessive erythrocytic destruction, the increased amount of urobilin absorbed by the intestine may not be taken care of by the normal liver and will appear in the urine. Some authors believe that the absorption of urobilin and urobilinogen and their conversion by oxidation into bilirubin in the liver represent the normal enterohepatic circulation of "bilirubin."

Bilirubin, bilverdin and urobilin are not toxic in ordinary amounts. Whether bilirubin and the other bile pigments have a function in animal economy has not been established. They are generally considered to be entirely excretory products.[2]

Cholesterol.—Bile is not the only secretion which contains cholesterol; it is found also in the sebaceous secretions and in the secretion or excretion of the small intestine. The cholesterol content of liver bile is always less than that of the blood; it ranges from 50 to 160 mg. per hundred cubic centimeters. Gallbladder bile contains more cholesterol, depending on the cholesterol content of the liver bile and the degree of concentration of the bile in the gallbladder. In the distended stone-free gallbladder of a pregnant woman the concentration of cholesterol may vary from 100 to 900 mg. per hundred cubic centimeters; in most cases the values ranged from 100 to 400 mg. for cholesterol and from 300 to 600 mg. per hundred cubic centimeters for bile salts.[15] In hepatitis the cholesterol output, like the cholic acid output, of liver bile is decreased.[16] Practically all of the cholesterol in bile is in the free, nonesterified form. All the evidence indicates that cholesterol is not excreted by the mucosa of the gallbladder,[1] except in the presence of pyogenic infection or hemorrhage.

The source of the cholesterol in the bile is unknown; whether it is an excretory product or serves some purpose in digestion is undetermined. Cholesterol can be synthesized in the body apparently by the coupling of many small molecules. It can be absorbed apparently from the intestine, particularly when fat and bile salts are being absorbed.[18] One might think it should be easy to determine whether dietary cholesterol affects the biliary cholesterol output. Yet, the literature is discordant on this point. The evidence indicates that in the dog and in man dietary cholesterol has little influence on the content of cholesterol in the bile. The cholesterol output in the bile of the dog is always increased when bile is returned to the intestine, as it usually is when ox bile salts are given orally.[17a] In regard to the formation of stones, the concentration of cholesterol in the bile is more important than the total output. It has not been demonstrated that the hypercholesteremia of diabetes, nephrosis, etc., increases the output of cholesterol in the bile or predisposes to cholesterol biliary calculi.

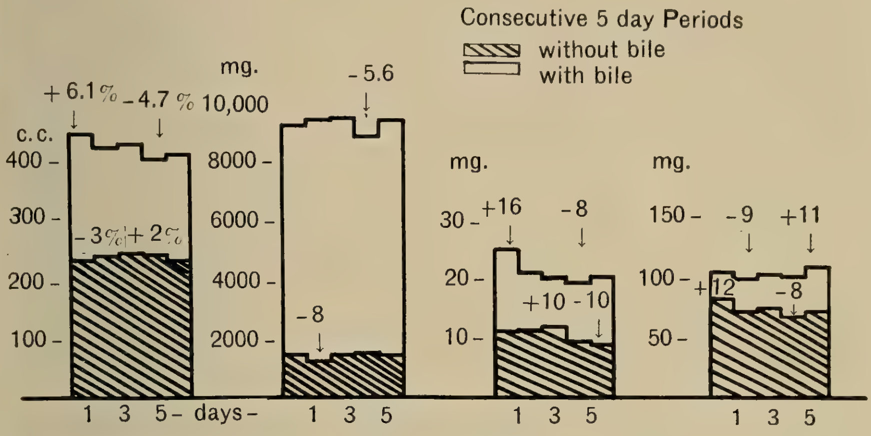

FIG. 88.—Chart showing the output of certain constituents of the bile for consecutive five day periods with and without the return of bile.

In regard to the fate of the biliary cholesterol, the evidence indicates that a portion may be absorbed and the remainder excreted in the feces[18] (Fig. 88).

Cholesterol in ordinary amounts given orally or given properly intravenously is not toxic; if it is given intravenously over a prolonged period, fatty liver may be produced, and in rabbits atheromatosis of the blood-vessels may occur.

The only function so far ascribed to the presence of cholesterol in bile is that it improves the emulsification of bile.

Lipids Other Than Cholesterol in Bile.—More fatty acid occurs in the bile, particularly the bladder bile, than in any other body fluid.[23] More fatty acid than complex phospholipids is present. Stearic, palmitic and oleic acid have been identified; in addition, such less volatile fatty acids as acetic, propionic and butyric acid have been found in human bile. The effect of diet on the fatty acid content is at present uncertain; however, it has been reported that the unsaturated fatty acids in the bile bear no strict relation to the unsaturated fatty acids in the diet.[12] If the human liver manifests fatty degeneration, it is reported that the bladder bile contains more lipid (2 per cent) than the normal average (0.83 per cent).[11] The soaps of fatty acids and phosphatides increase the emulsifying properties of bile salts, which explains why hepatic bile is usually a clear, limpid fluid, regardless of its high lipid content.

Space does not permit comments regarding the presence of the other organic and the inorganic substances in bile and the factors which modify their output.

Functions of Bile.—The Digestive Functions.—Bile augments intestinal motility and may be used as a laxative. It serves as a conferment in the digestion of fat and assists emulsification and saponification. Because of its bile salt content, it facilitates the absorption of fat and probably of cholesterol. The clay-colored stools of obstructive jaundice are due not only to the absence of pigment but to an excess of fat and soap. Bile salts are necessary for the adequate absorption of carotene, the precursor of vitamin A, and of vitamins D, E and K. Bile salts facilitate the absorption of iron and calcium. When fat is not properly absorbed, insoluble calcium soaps tend to be formed and excreted in the feces. Bile probably has some antiseptic or bacteriostatic effect on the internal flora, and it has some effect in the neutralization of the acid chyme coming from the stomach.

Effects of the Absence of Bile From the Intestine Over Prolonged Periods.—The effects of the total absence of bile from the intestine over prolonged periods have been most closely observed in dogs with biliary fistula. The abnormalities are as follows: (*a*) an intestinal disturbance chiefly characterized by a loss of appetite and weight, (*b*) duodenal and occasionally gastric ulcer, which may be chronic and hemorrhagic or acute and perforating, (*c*) anemia, (*d*) a purpuric tendency with spontaneous bleeding and (*e*) osteoporosis. The first three abnormalities are most likely to be associated with a low grade or acute hepatitis. Yet, all the abnormalities may be explained by the absence of the digestive functions of bile just listed, and they may be prevented by the frequent return of some bile or bile salts and adequate feeding of liver. Concrements consisting chiefly of calcium bilirubinate[5] will, after several months, collect in the biliary drainage tubing, even when mild suction is continuously applied to the tubing. Bile salts, by keeping the bile thin and moving, definitely tend to prevent concrements from forming and hepatitis from developing. A review of the literature on the effects of complete biliary fistula in man reveals that effects similar to those seen in the dog may occur;[20] some patients have lived several years, but the completeness of the fistula in such cases is problematic. The disturbances incidental to obstructive jaundice have been reviewed[6] and will not be discussed here. Death in obstructive jaundice is due to hepatic insufficiency associated with renal impairment and a general metabolic breakdown.

General Points of Interest.—The secretory pressure of bile ranges from 30 to 35 centimeters of water or bile pressure. Less pressure, *e. g.*, 20 or 25 centimeters, will result in hyperbilirubinemia.

Bile is still formed after all the portal blood is shunted into the vena cava, but is decreased about 50 per cent in volume. Ligation of the hepatic artery near its origin temporarily increases the volume output of bile; the permanent effect is undetermined. An increase in intrahepatic vascular pressure from any cause decreases the formation of bile and may stop it completely. In a markedly congested liver with acholia even bile salt (decholin) given intravenously will not cause a flow of bile.[19]

Secretin is a true choleretic, increasing the volume output of bile.[8]

The vagi exert both an inhibitory and an excitatory secretory effect on the liver.[19] When the subject is stimulated psychically by sham feeding, only 1 or 2 cubic centimeters of bile results, an effect like that on the pancreas. The splanchnic nerve fibers exert entirely an inhibitory effect, which is probably due to vasomotor changes in the liver. Complete cessation of bile flow can be produced when the bile is flowing slowly, and a marked decrease when it is flowing briskly after administration of bile salt, by stimulating the splanchnic nerve or the hepatic nerves. Bile flow can also be reflexly diminished, when the bile is flowing without bile salt stimulation, by distention of the proximal colon and by stimulation of the pelvic nerves or the inferior and superior mesenteric ganglions. This reflex inhibition of bile formation is abolished by section of the hepatic nerves.[3] An increase in blood flow without an increase in intrahepatic vascular pressure, as produced by slight elevations in temperature induced by diathermy, increases volume output.[13] The injection of dehydrocholic acid (decholin) intravenously (fifteen to twenty minutes) increases the rate of hepatic arterial blood flow temporarily.[13]

"White Bile."—When a portion of a hepatic duct is doubly ligated, a clear, colorless, viscid though rather thin secretion collects between the ligatures. When the cystic duct is occluded and the gallbladder does not become infected, the biliary constituents are gradually absorbed and a clear to opalescent viscid fluid, "hydrops bile," collects. These secretions represent the secretion of the epithelium of the bile ducts and gallbladder. When the common duct is occluded with the gallbladder removed or rendered functionless by disease, a clear to lightly pigmented fluid ("a white or colorless system") is present in the dilated ducts. For several weeks after common duct obstruction with a normal gallbladder in place, the content of the distended gallbladder is green or dark ("a green system"). After the development of considerable cirrhosis of the liver, the bile is lightly pigmented. In high grade toxic or infectious hepatitis the bile is only lightly pigmented. In hemolytic icterus the bile is generally dark and thick, owing to excessive pigment.

"Milk of Calcium Bile."—In the presence of cystic duct obstruction in man and animal, a fluid resembling milk or thick "whitewash" is occasionally found in gallbladder. It consists of suspended particles, chiefly of calcium carbonate. Some unknown pathologic disturbance other than simple cystic duct obstruction is requisite for the production of such fluid. At times the gallbladder cavity may be almost entirely filled with a deposit of solid calcium carbonate.[14]

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GALLBLADDER AND BILE DUCTS

General Functions.—The gallbladder manifests three activities, namely, absorption, secretion and movement.[7] The general functions assigned to the gallbladder are: (*a*) to serve as a pressure regulatory mechanism, and (*b*) to serve as a bile reservoir for digestive purposes. The importance of the first function is supported by the following facts: 1. The sphincter of Oddi is essential for the filling of the gallbladder. 2. In some animals the secretory pressure of bile is much less than the pressure necessary to overcome the sphincter. To prevent injurious back pressure when the sphincter is vigorously contracted, a regulatory device is necessary. 3. Cholecystectomy in animals that have a relatively powerful sphincter leads usually to dilatation of the extrahepatic ducts. 4. Those animals which do not possess a gallbladder physiologically have no sphincter or a weak one. Thus, when a gallbladder is present an efficient sphincter is necessary for filling, and when an efficient sphincter is present a gallbladder is necessary fore regulation of pressure. This would suggest that the gallbladder developed in the evolutionary process concomitantly with the appearance of the sphincter. The evidence in support of the second general function is less satisfactory, but the following facts force its consideration: 1. All reptiles and amphibians, animals which feed intermittently, have a gallbladder. 2. Carnivorous mammals (except whales) have a gallbladder, while some mammals with other dietary habits have lost the organ. Herbivorous forms with continuous feeding habits and digestion are most likely to lack the organ. 3. All domestic animals that form a small quantity of bile have a gallbladder of large storage capacity, and animals which do not possess the organ or possess one that does not concentrate well and can store relatively little of the hepatic output of bile form large quantities of thin bile. 4. Bile plays an important role in digestion and absorption, and hence in animals that do not form large quantities of bile and feed intermittently a storage reservoir for the bile formed between meals would be important.[13] The practical import of this second function of the gallbladder is that in cholecystectomized subjects or subjects with chronic biliary tract complaints the bile should be kept thin and flowing; this may be accomplished by giving four protein-containing meals a day and oral administration of bile salts.

Absorption.—In the process of the four to ten fold concentration of the liver bile in the gallbladder, chiefly water and inorganic salts are absorbed, and the slightly alkaline liver bile is slightly acidified. The bile acids render the fats and cholesterol soluble in an acid-aqueous solution. The normal human organ, because of its concentrating ability, can store the twelve to twenty-four hour fasting output of bile. This is why bilirubinuria develops sooner in cholecystectomized than in normal dogs. The acutely inflamed gallbladder does not concentrate, nor does it evacuate; also, it may not receive liver bile because of inflammatory obstruction of the cystic duct. After the inflammation has fully subsided, the gallbladder may again concentrate and evacuate; but if the inflammation becomes chronic or if the gallbladder wall is thickened (fibrosis), the organ does not concentrate or, if so, only slightly. The gallbladder with hyperplastic rugae concentrates exceedingly well unless it is inflamed. Hyperplasia of the mucosa appears to be due to stasis in the viscus.[4] In the presence of obstruction of the cystic duct without inflammation, the gallbladder may in a few weeks absorb all or most of the constituents of bile. The extrahepatic bile ducts do not concentrate to a significant extent; however, in an isolated segment the pigments and cholates disappear in a week or more. In the ducts secretion exceeds absorption.

When tetraiodophenolphthalein is given to subjects for the purpose of visualizing the gallbladder (rendering it opaque to *x*-rays), the dye is eliminated in the liver bile and is concentrated by the gallbladder if the organ is normal. The maximum concentration is reached from twelve to fourteen hours after administration of the dye.

Secretion.—The mucosa of the gallbladder and ducts secretes normally a mucoid, albuminous fluid. It is thought that the glands of the neck of the gallbladder may secrete some true mucin. The normal rate of secretion of the gallbladder is unknown, though 20 cubic centimeters of clear, viscous fluid has been collected per day from the non-infected fistulous organ with cystic duct obstruction. This secretion is analogous to non-infected "hydrops bile." In the presence of an unknown type of disease, a "milk of calcium bile" may be found in the gallbladder.

Movement.—The motor activity of the gallbladder[7] is of two types: (1) rhythmic tonus changes amounting to from 1 to 3 centimeters of bile pressure, which may be augmented in rate and amplitude by any mild adequate stimulation, and (2) tonic contraction of the musculature of the gallbladder as a whole (Fig. 89). The gallbladder of the dog by contracting may exert a pressure of from 20 to 30 centimeters of bile. The force of contraction of the human gallbladder has not been measured, but the organ has been seen by direct vision to contract and evacuate. It is interesting that stones located in a group in the fundus of the gallbladder may line up in columns after the ingestion of a fatty meal.

It is obviously significant that the power of the normal gallbladder to contract is not greater than the secretory pressure of bile. The gallbladder of some patients appears to have a hypertrophied musculature (work hypertrophy). To what this is due and whether such a gallbladder may exert successive pressure are not known, but hypertrophy has been seen in dogs with a stricture of the common duct.

The chief stimulant of gallbladder contraction thus far discovered is the hormone cholecystokinin. The stimulation of nerves has never been observed to have more than a slight and temporary effect on gallbladder evacuation.

The hormone may be extracted from the duodenal mucosa and, when injected intravenously, causes a more or less prolonged contraction of the gallbladder, with evacuation (Fig. 90). It has been demonstrated to operate physiologically by cross-circulation and transplantation experiments in the dog and by blood transfusion experiments in man.

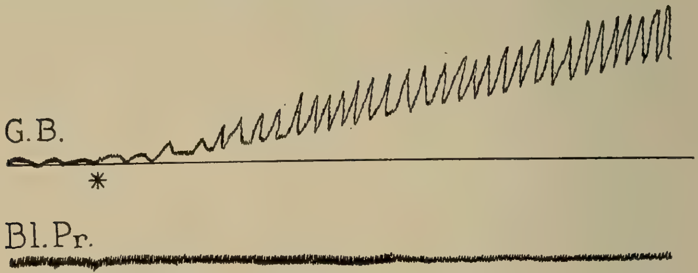

Fig. 89.—Diagram showing the response of the dog's gallbladder to the duodenal administration of slightly acidified pancreatic digested egg yolk and cream. *G.B.* indicates gallbladder pressure; *Bl.Pr.*, blood pressure. Note the increase in rate and amplitude of the tonus rhythm and the gradually increasing "tonic" contraction.

The most effective excitants of hormone production are acids and fats acting in the upper part of the intestine. All fats are effective, but egg yolk and cream appear to be the most active. Proteins, particularly meat, rank next, and carbohydrates have no significant action.

After the gallbladder has been visualized, the fatty meal most commonly employed to empty the organ is the "Boyden meal," which consists of four egg yolks mixed with an equal volume of milk and sweetened with sugar.

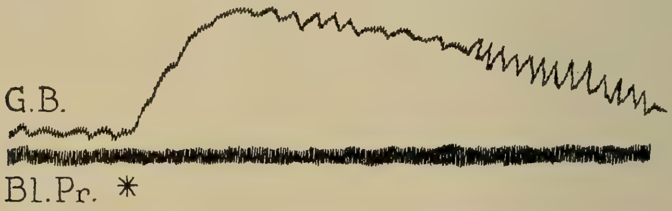

Fig. 90.—Diagram showing the response of the dog's gallbladder to cholecystokinin. *G.B.* indicates gallbladder pressure; *Bl.Pr.*, blood pressure. The contraction from the single dose lasted for twenty minutes.

Evacuation.—Those investigators who have devoted considerable time to the study of evacuation consider the gallbladder and sphincter of Oddi as a functional unit.

Boyden,[2] who has studied by a quantitative method many "normal" human subjects, recognized three types of gallbladder response to a fat meal. In the first type, a primary relaxation of the gallbladder results, with what appears to be a closure of the sphincter. Only a temporary delay in emptying occurs. This type is relatively rare. In the second type, which is more common, contraction and evacuation start quickly, with simultaneous relaxation of the sphincter, and evacuation occurs rapidly. These two types comprise the larger group of subjects, evacuation being complete (95 per cent) in two hours. In the third type, evacuation starts but after an interval stops. Then filling of the gallbladder occurs. Further, evacuation occurs in successive phases. Boyden expressed the opinion that in this type the sphincter is primarily concerned in stopping the evacuation and starting the filling, since the speed of the initial evacuation is normal. A slight evacuation of the gallbladder may occur in about 10 per cent of persons on smelling food. A spontaneous evacuation occurs rarely and probably in response to a stretch stimulus. If the organ is distended or contracted too much, it does not respond as well to cholecystokinin. The contractibility of the organ is reduced if it is stretched with a pressure of 30 centimeters of bile for one hour or more. The large undistended gallbladder, however, frequently evacuates at a normal rate.[3] The nerve supply of the gallbladder in higher mammals plays a very minor role in effecting evacuation.

Boyden and Grantham[3] have found that the gallbladder of the female empties at a rather constant rate from childhood to old age. In the male some factor begins to operate at puberty to slow down the rate, so that it empties more slowly than the viscus of the female. If the biliary tract escapes disease, its motility is not impaired by age. In these studies about 75 per cent evacuation was obtained in forty minutes. The gallbladder during pregnancy is usually distended and tends to evacuate more slowly than ante or post partum.[12] Thus, the greater susceptibility of women to gallbladder disease is not due to a constitutionally inferior gallbladder but to external factors which affect the sphincter of Oddi and the musculature of the gallbladder reflexly or modify the bile.

The action of many *drugs* on the musculature of the gallbladder has been studied. Cholecystokinin has proved to be the most powerful gallbladder motor excitant discovered and produces no side actions, such as a fall or a rise in blood pressure.

Atropine relaxes the gallbladder but does not abolish the action of cholecystokinin. Morphine, when effective, increases the tonus rhythm of the gallbladder. Pilocarpine may cause some expulsion of bile from the gallbladder into the ducts, but it does not cause evacuation, owing to its augmentation of sphincteric and duodenal tone. Solution of pituitary after a latent period of ten or fifteen minutes causes the gallbladder to contract and frequently to evacuate from one-fourth to one-half of its contents. However, solution of pituitary is not as effective as egg yolk and fat.

Surgical operations, such as gastroenterostomy, gastric resection and pyloroplasty, do not decrease the efficacy of egg yolk in provoking gallbladder evacuation. However, the ejection of egg yolk into the middle or lower part of the ileum has no effect on the gallbladder. During the first day or two after operations on the upper part of the abdomen the gallbladder may manifest a rather marked atonic distention. In patients with "peptic" ulcer the gallbladder frequently evacuates faster than normal, though the opposite may obtain.

Failure of Visualization.—A failure to visualize the gallbladder may be due to: (*a*) failure of hepatic elimination of the dye, (*b*) failure of the gallbladder to concentrate, (*c*) obstruction of the cystic duct, (*d*) incompetence of the sphincter of Oddi or (*e*) poor intestinal absorption of the dye.

Failure or Retardation of Evacuation.—The causes of stasis are: (*a*) hypertonic sphincter of Oddi, (*b*) inflamed ampulla, (*c*) obstructed common duct, (*d*) hypertonic and inflamed duodenum, (*e*) reversed peristalsis of the duodenum, (*f*) inadequate diet, low in fats, protein and fruit juices, (*g*) narrow and much convoluted or inflamed cystic duct, (*h*) acutely inflamed gallbladder or (*i*) impaction of stones in the cystic duct. The slow evacuation in pregnancy may be due to: (*a*) reflex hypertonus of the sphincter of Oddi, (*b*) reflex inhibition of the gallbladder, (*c*) sex hormone action on the gallbladder, (*d*) the presence of very thick bile, due either to reflex inhibition of bile secretion from the alimentary tract or pelvic viscera, which first affects water content, or to an actual increase in the elimination of solids by the liver. Stasis in the gallbladder promotes hyperplasia of the gallbladder mucosa and lymphoid tissue and lipoid deposition in the mucosa.

The Sphincter of Oddi, or Intramural Resistance.—Whether the gallbladder will evacuate when stimulated depends on the tone of the sphincter of Oddi or duodenum or the intramural resistance offered to the flow of bile from the common duct into the lumen of the duodenum. I shall hereafter designate the intramural resistance as being due solely to the sphincter of Oddi, which is true only in part. (For a recent anatomic consideration of the sphincter choledochus and valves of Heister, see References 8 and 19 in section on bile.)

The sphincter of Oddi can resist up to 75 centimeters of bile pressure, whereas the maximum expulsive pressure of the normal gallbladder is 30 centimeters. Hence, it is possible for a spastic or hypertonic sphincter to prevent gallbladder evacuation. The average resistance of the sphincter in man is about 15 centimeters of water pressure. In cholangitis secondary to the presence of a stone, the sphincter is frequently irritable and may remain so for weeks. In such a condition the sphincter may manifest resistance above 50 centimeters of water, which, however, is subject to considerable fluctuation and is usually not stabilized at a high level.[1]

Summary.—The points of chief interest pertaining to the physiology of the sphincter will be listed: 1. Removal of a normal gallbladder causes the sphincter to become incompetent for varying periods. This shows that the gallbladder has a functional relation to the sphincter. The cause of the dilatation of the ducts is uncertain. 2. Any procedure which increases the tone of the duodenum retards the flow of bile into the duodenum. 3. Any procedure which decreases the tone of the duodenum and promotes normal peristalsis favors the flow of bile into the duodenum. 4. The vagi are the nerves predominantly concerned in increasing the resistance to the flow of bile into the duodenum. The innervation of the sphincter is not simple. For example, spinal anesthesia decreases sphincteric resistance. 5. The evidence indicates that when the gallbladder contracts the sphincter relaxes, but not completely. After the injection of cholecystokinin, the hormone formed when fats and acids particularly come into contact with the upper part of the intestinal mucosa, the sphincter relaxes, while the gallbladder contracts. 6. In some human subjects, during digestion, after the gallbladder has started to empty, the resistance of the sphincter will increase and the gallbladder start to fill. This causes the gallbladder to empty in phases. 7. A fatty meal generally decreases the sphincteric resistance slightly, whereas a carbohydrate meal has no significant effect.

8. Atropine decreases the resistance to the flow of bile into the duodenum. Pilocarpine has the opposite effect. These drugs in ordinary doses have but little effect in man. 9. Morphine, pantopon, dilaudid and codeine increase sphincteric resistance. Hyoscine, papaverine, prostigmine, calcium salts, pituitrin and phenobarbital have no significant effect. The effect of ephedrine is variable. 10. Nitroglycerin and especially amylnitrite relax the sphincter. Theophylline decreases resistance. 11. Bile salts (decholin intravenously) tend to decrease the resistance slightly. 12. Magnesium sulfate, sodium sulfate and magnesium oxide in the duodenum tend to decrease the resistance. There is no real evidence showing that magnesium sulfate in the duodenum causes the gallbladder to contract; the gallbladder empties to some extent, but this is probably due solely to relaxation of the sphincter. Concentrated magnesium sulfate in the duodenum may relax a spastic sphincter.

Disturbances of Gallbladder.—A Spastic Sphincter May Cause "Biliary Tract Pain."—A spasm of the sphincter (sphincterismus) in the presence of a contracting gallbladder produces biliary colic in man. Biliary colic may occur after an injection of cholecystokinin when little or no bile is flowing into the duodenum owing to a spastic sphincter. It may follow the injection of pilocarpine when the gallbladder is contracting in response to fat. (Pilocarpine causes the sphincter to contract.) In patients with a tube in the cystic or the common duct, if the sphincter if spastic, distention of the ducts from 16 to 30 centimeters of water pressure will cause typical biliary tract pain. This shows that in the presence of a spastic sphincter, pain may be elicited by the degree of pressure that may result from a vigorous contraction of the gallbladder. In this connection, pain may be experienced in a cholecystectomized patient with obstruction of the ampulla when decholin, a bile salt, is injected intravenously. In other words, the secretory pressure of bile (30 cm. of water) suddenly exerted on the bile ducts is also adequate for the production of pain.[8]

Whether the nerve endings of the biliary tract must have been previously sensitized by some preëxisting condition for pain to occur is not known. But it is known that pain can be produced in a presumably normal person whose gallbladder is visualized and evacuates according to normal standards. The time factor is important; the slow distention of any viscus is less likely to cause pain than its sudden distention. Slow distention is more likely to cause a sensation of distention, ache and tenderness.

Biliary Dyskinesia or Dyssynergia.—On the basis of the preceding facts and considerations it is obvious that disturbances of the sphincter of Oddi or of the choledochoduodenal mechanism may play an important role in the causation and symptoms of biliary tract disease. In fact, a number of well known clinicians and surgeons believe in the existence of a disordered motor state, which also involves the gallbladder either directly or indirectly and has been called biliary dyskinesia or dyssynergia.[9] When a patient complaining of biliary tract distress has a gallbladder that may be visualized well and then on taking the fatty meal manifests visualization of the hepatic ducts, some abnormality of the sphincter or ampulla should certainly be suspected.

Westphal's classification of biliary dyskinesia follows:

1. Hyperkinetic.
    a. Hypermotile. Increased motility of the gallbladder with very rapid emptying in response to fat.

b. Hypertonic. Contraction of the gallbladder against spasm of the sphincter with spastic distention and mild colicky pain.

2. Atonic.

Relaxation or atony of the gallbladder with spasm of the sphincter causing atonic distention of the gallbladder with mild continuous heavy aching sensation or sensation of tumor.

Hypertrophy of the Sphincter.—It is of interest that hypertrophy of the sphincter may occur. This has been reported by a number of observers.[5] The cause is not known. It has been found in patients who have had cholecystitis or duodenal ulcer.

Explanation of Certain Symptoms Associated With Biliary Tract Disturbances.—The vagi carry afferent impulses responsible chiefly for anorexia, nausea and vomiting when the gallbladder and ducts are distended. The splanchnic nerves carry pain impulses when the ducts and gallbladder are distended.[14] Gastric flatulence is not likely due to gastric anacidity and fermentation but is due to loss of tone of the gastric musculature and aspiration or swallowing of air, which may be demonstrated by the proper distention of the gallbladder in dogs.

Reflex Disturbances of the Biliary Tract.—Clinical evidence indicates that "constipation" and bowel spasm contribute to stasis or malfunction of the biliary tract. Cholecystopathy is frequent in women who have borne children. The incidence of lesions of the gallbladder in persons above forty is doubled in the presence of diverticula of the colon.[10] In the presence of cholecystitis and colonic dysfunction it has been found that the gallbladder may be visualized and will empty in 44 per cent of cases after ten days of bowel management,[11] which shows how important it is to eliminate colonic dysfunction before evaluating the condition of the gallbladder. The same is true in some cases of duodenal ulcer and so-called chronic appendicitis. It remains to be determined definitely whether these disturbances in the alimentary tract reflexly affect the liver, gallbladder or sphincter. Preliminary evidence indicates that all three are affected in the dog.[6]

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CHAPTER XVIII

DISEASES OF THE LIVER

The liver is one of the most important organs in the normal and abnormal function of the gastrointestinal tract. Hepatic disorders inevitably affect the digestive system. It is only in recent years that the liver has been given its proper place as a factor in many evident and obscure digestive complaints. A great deal of valuable experimental work has been done on the pathologic physiology of the liver, indicating the tremendous reserve function of that organ and its capacity for regeneration and repair. It is the purpose of this chapter not to present a discussion of the common diseases of the liver, which may be found in any standard textbook on medicine, but to discuss the newer manifestations, recent diagnostic data and the modern therapeutic approach to the problems concerned in hepatic derangements. The anatomy of the liver and gallbladder has been admirably discussed by De Garis. The physiology of the liver and gallbladder has been amply covered by Ivy. The association of the gallbladder and the liver has been alluded to by Gaither, and the relation of the pancreas and the liver, by McClure and Jankelson. Therefore, I shall try to avoid any repetition of statements made in these splendid contributions.

LIVER FUNCTIONS

The liver manifests many functions. Considering its many activities, its large factor of safety and its regenerative capacity, it is able to withstand repeated insult without showing at times corresponding demonstrable clinical evidence.

Therefore, no one functional test at the present time is of absolute diagnostic value, and one may have to relay on the results of several tests. It is well known that one single test may give normal results while others reveal marked impairment.

Since all the liver functions are manifestations of metabolic activities of the liver cells, they are necessarily interrelated and are valid indexes of the physiologic integrity of those cells. It is of clinical importance, as Mann[33] recently emphasized, to recognize that the functioning ability of the liver is constantly changing, so that repeated tests are necessary to obtain an index of improvement or failure in the liver. The following tests are arranged to facilitate discussion of the physiologic functions of the liver as well as the excretions of substances which are foreign to the liver cell.

Carbohydrate Metabolism

Dextrose Tolerance Test.—The fasting blood sugar level may be high in liver disease, or it may be low, especially with marked destructive lesions. The dextrose tolerance curve in the presence of toxemic liver damage or early hepatitis is distinguished with difficulty from the curves present with mild diabetes mellitus, for which the usual tolerance tests are done. Other clinical or laboratory evidence of liver dysfunction may help to place the responsibility for the diabetic type of curve obtained, but cannot rule out the possibility of coincidental liver damage and diabetes mellitus. Clinically this differentiation is important for therapeutic and prognostic reasons. From a physiologic standpoint, the diabetic dextrose tolerance curves due to hepatitis and to diabetes present certain similarities and certain differences. They are similar because both result from a failure in operation of the homeostatic mechanism of the liver for the maintenance of a constant blood sugar level.[50] They differ in the manner in which the homeostatic mechanism is disturbed. In diabetes the mechanism fails because of a disorder of its endocrine regulators: the threshold of stimulation of the mechanism is infinitely high, and the liver continues to pour sugar into the blood despite the influx of exogenous sugar, which would ordinarily inhibit it. In hepatitis the threshold of stimulation of the hepatic mechanism may not be significantly elevated, but the mechanism is sluggish or unresponsive to its usual stimulus.[51] This difference between diabetes mellitus and hepatitis often makes it possible to distinguish between the two, by a comparison of the dextrose tolerance curves obtained with large and small doses of sugar. In diabetes, the dose of sugar used for the test, no matter how large, still fails to raise the blood sugar level high enough to inhibit the liver. Thus, the larger the test dose, the more diabetic the tolerance curve obtained. Soskin and Mirsky[52] have shown, however, that a damaged liver which fails to respond to a small dose of sugar may still yield a normal response to a large test dose, which represents a more adequate stimulus to its unresponsive mechanism. In hepatitis, therefore, one may obtain a diabetic type of curve with a small test dose and a normal dextrose tolerance curve with a large dose of sugar.

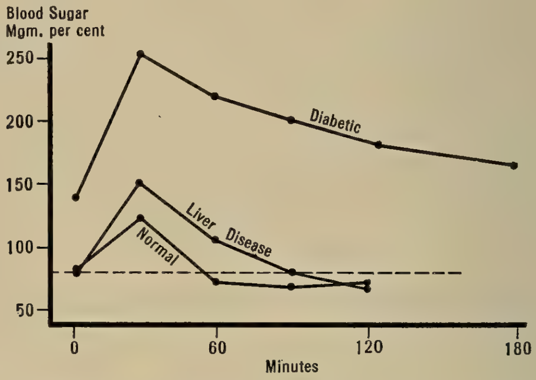

FIG. 91.—The average intravenous dextrose tolerance curves of 30 normal control individuals; 25 patients with the mildest diabetes mellitus available; and 50 patients with proved mild or early liver disease. The normal curve returns to the preinjection level by sixty minutes; the hepatic curve, after sixty and before one hundred and twenty minutes; the diabetic curve, after one hundred and twenty minutes. (Soskin, *Clinics*, courtesy of J. B. Lippincott Co.)

Soskin[49] has recently described a dextrose tolerance test that produces a result characteristic of liver disease and distinguishes it easily from diabetes mellitus. Dextrose in 50 per cent solution, in a dose of 0.33 Gm. per kilogram of body weight, is injected intravenously within three to five minutes when the patient has fasted for twelve hours. Blood samples are taken before and at one-half, one and two hours after injection. Blood is obtained by finger puncture, and the blood sugar is determined by the micromodification of the Somogyi-Shaffer-Hartman method. Normal controls show a return of the blood sugar to the preinjection level before sixty minutes, when the blood sugar in patients with liver disease usually is still definitely above this; it does return to that level in two hours, however. In patients with diabetes mellitus, the blood sugar is still elevated after two hours. However, where the investigator is familiar only with the venipuncture method, the test may be performed on samples of venous blood, using the identical technic.

The oral dextrose tolerance test advocated and modified by Jacobi[23] and others is subject to the same variations and criticisms as the oral administration of dextrose in the evaluation of diabetes mellitus. One must always be absolutely certain that the absorption from the intestinal tract is uniform and that there is no impairment of cells in the small intestine, which would invalidate the test.

The Galactose Tolerance Test.—The galactose tolerance test is based on the assumption that the liver alone changes galactose to glycogen. Any impairment of this function causes galactose to appear in the urine. Galactose is administered either by mouth or intravenously. In the oral test, after over-night fasting, the patient empties his bladder, and the specimen obtained is saved as a control. He then drinks a solution of 40 Gm. of galactose in 500 cubic centimeters of water flavored with a few drops of lemon juice. Thereafter he may drink water freely. Specimens of urine are collected at hourly intervals during the next five hours, each specimen being tested with the Benedict qualitative reagent for reducing substances. The samples giving positive results are mixed, and the total reducing substance is determined by the quantitative method of Benedict. A total output of galactose exceeding 3 Gm. constitutes a positive test.

Banks and his associates,[3] investigating 127 cases of proved hepatic disease, found variable results; for instance, 15 of 18 patients with acute or subacute jaundice (intrahepatic) excreted 3 Gm. or more of galactose during hospitalization, while 13 patients with various types of portal and biliary cirrhosis had consistently normal galactose tolerance, with an excretion of between 2 and 3 Gm. Of 20 patients with proved carcinoma of the head of the pancreas or ampulla of Vater, only 9 showed increased galactose in the urine. Jaundice in these cases ranged in duration from three days to six months. Five of 10 patients with primary neoplasm of the common or hepatic ducts gave positive results. Three of 7 patients with obstructive jaundice resulting from metastatic malignant deposits in the liver excreted galactose in excess of 3 Gm. Positive galactose tests were obtained in 46 per cent of 37 cases of proved jaundice secondary to malignant disease. Positive tests were obtained in 33 per cent of 38 cases of jaundice due to choledocholithiasis, cholecystitis with stones, associated hepatic lesions and stricture of the common or hepatic ducts. Bensley[5] reviewed the results of this test in 684 patients with jaundice and found that, while 81 per cent of patients with obstructive jaundice excreted 3 Gm. or less, only 30 per cent of those with hepatocellular jaundice gave similar results.

The errors that accrue from this test are probably due to malabsorption of galactose caused by gastric stasis, delay in absorption secondary to passive hyperemia of the gastrointestinal tract present in certain types of chronic hepatic diseases, faulty excretion of sugar due to renal and vesical factors, oliguria caused by dehydration or by acute renal injury associated with primary hepatic lesions, functional retention of urine in the bladder and the residual urine of a hypertrophied prostate gland. Care should be taken in the interpretation of this test when the patient is in a state of dehydration or starvation, or in the presence of diabetes or thyrotoxicosis. Furthermore, when dextrose is given to repair liver damage, increased utilization of galactose by the liver also may occur. With the oral test, an excretion of 6 Gm. or more may indicate an intrahepatic jaundice more often than an obstructive jaundice and should be a factor considered before surgical intervention. In acute hepatic injury there is usually an increased excretion of galactose. In chronic hepatic injury there may be variable results from the administration of galactose; as the liver regenerates, the test tends to become negative.

The Intravenous Method.—After a twelve hour fast, after which a venous blood sample is withdrawn, 100 cubic centimeters of a properly warmed, sterilized and buffered 25 per cent solution of galactose is injected slowly. Subsequently samples of blood are taken at intervals of sixty, seventy-five and ninety minutes. From these samples a Folin and Wu tungstic acid is prepared. The fermentable reducing substance is determined by the technic of Somogyi. The amount of nonfermentable reducing substance is determined by the method of Folin and Wu. The difference between the nonfermentable reducing substance in the first sample of blood and the samples taken after the injection of galactose, divided by 0.75 (for the difference between dextrose and galactose reduction), represents the galactose retained in the venous blood. Patients without liver or biliary tract disease have shown complete utilization of 25 Gm. of galactose within one hour, thus establishing the standard of normality.

Jankelson and his associates[24] have shown that a retention of intravenously injected galactose is found in patients with hepatitis, whether toxic or infectious, except subsiding catarrhal jaundice. In 10 cases studied there was a variation from 2.3 to 13.3 mg. in the galactose retained per hundred cubic centimeters of blood plasma sixty minutes after injection. Observations at seventy-five and ninety minutes revealed a retention of galactose of from 0 to 10.1 and from 0 to 2.6 mg. per hundred cubic centimeters of blood plasma, respectively. Tests of 6 patients with obstructive jaundice gave positive results in 50 per cent one hour after injection. Seventy-five minutes after injection patients with obstructive jaundice revealed a retention of galactose of 0.7 mg. per hundred cubic centimeters; patients with intrahepatic jaundice revealed a retention of galactose of 2.7 mg. per hundred cubic centimeters. At sixty and ninety minute intervals the tests in both groups revealed the same degree of retention.

Of 25 patients with portal cirrhosis, positive tests were obtained for 16 and negative for 9. Patients with cholecystitis gave negative results. However, positive results were obtained in 1 of 2 cases of cholelithiasis. In portal cirrhosis the test was positive in 64 per cent of cases. In the authors' experience, cirrhosis of the liver with ascites invariably gives a positive test, whereas cardiac ascites persistently gives negative results.

Bassett and associates[4] used a dose of 0.5 Gm. of galactose per kilogram of body weight and 50 per cent solution. They found no galactose in the blood at seventy-five minutes in normal patients, and suggested that any retention after sixty minutes may be abnormal. Seventy-five minutes after injection they found the blood galactose to be greater than 20 mg. per hundred cubic centimeters in 81 per cent of cases of hepatotoxic jaundice and less than 20 mg. in 82 per cent of cases of obstructive jaundice of less than six months' duration.

The Levulose Tolerance Test.—The levulose tolerance test is based on the observation that the value for blood sugar is normally unaffected by the oral administration of levulose, whereas it is increased in the presence of hepatic disease. A standard dose of 40 Gm. of levulose may be administered in 20 cubic centimeters of lemonade, the fasting blood sugar value taken and the subsequent blood sugar level determined one and two hours after the administration of levulose. An increase of more than 30 mg. per hundred cubic centimeters in the value of the blood sugar is considered a positive test. According to Snell and Magath,[47] a low initial value for fasting blood sugar, a mild diabetic tendency and chronic pancreatic disease tend to vitiate the results. Stewart and his co-workers[54a] found in their observations on this test a considerable variation between the results and the clinical picture of the patient. Recent modifications[21] of the test were devised in which the levulose tolerance curve is followed at half-hour intervals for two hours after ingestion of 50 Gm. of levulose. A rise of blood levulose equal to or less than 10 mg. per hundred cubic centimeters is normal; up to 15 mg. may be normal, and more than 15 mg. is abnormal. Rennie[54b] used a rise of more than 15 mg. in one hour as abnormal. This test, while it has some clinical application, is not of enough significance to warrant use.

The Sodium d-Lactate Clearance Test.—The liver converts d-lactate to glycogen, and, according to Soffer,[48] a diseased liver does so more slowly. The patient is put to bed and fasts for twelve hours, and then 75 mg. of sodium d-lactate per kilogram of body weight (12 to 14 per cent solution) is injected intravenously. A control blood sample and a thirty minute blood sample are taken into sodium fluoride anticoagulant, and the lactic acid content of the samples is determined. A retention of 50 mg. per hundred cubic centimeters of lactate above the control value indicates hepatocellular damage. The test is negative in cases of obstructive jaundice and, since it is expensive, is advocated mainly to enable differentiation between obstructive and hepatocellular jaundice when this is difficult. For this purpose it has yielded 90 per cent correct diagnosis, a much higher degree of accuracy than has been obtained by the oral hippuric acid, the oral galactose tolerance and urinary excretion of galactose and the urobilinogen test (Cohn).[48]

Fat Metabolism

Blood Cholesterol and Cholesterol Esters.—The exact role of the liver in cholesterol metabolism is not known, but liver damage has been found clinically to be associated with definite changes in the blood cholesterol. Recent studies have shown a wide range in the total blood cholesterol in normal persons, from as low as 109 mg. to as high as 392 mg. per hundred cubic centimeters. Despite this wide physiologic range, the level in the blood of any given individual is fairly constant. During obstructive jaundice the total cholesterol of the blood increases for some unknown reason; in general, hypercholesterolemia parallels the degree of increase of bile pigment. With damage to the liver cells the total blood cholesterol may be normal, elevated or subnormal, despite hyperbilirubinemia.

Normally, according to Sperry,[53] between 70 and 75 per cent of the cholesterol in the serum is present in the form of esters. The older literature held the cholesterol ester percentage to be much lower, and Kirk and his associates[26] (1935) found a range of 22 to 72 per cent in normal persons. Most other investigators, however, have confirmed the work of Sperry.[53] Thannhauser and Schaber[57] in 1926 reported a decrease in the cholesterol ester percentage in liver disease, and recent studies have confirmed these findings.

Apparently differences in the technic used in determining the cholesterol ester value have caused various investigators to use different criteria for the normal limits of the ester fraction. At the Michael Reese Hospital a large series of determinations showed the normal value for the cholesterol esters to be between 66 and 72 per cent of the total serum cholesterol.

My own experience at the Michael Reese Hospital has led me to believe that the cholesterol ester percentage is a valuable criterion of liver disease. The lowering of the esters is a good index of the severity of the parenchymatous liver damage, especially in acute disease. Contrary to the experience of Shay and Fieman,[45] White and associates,[62] as well as Greene and his co-workers,[16] found the cholesterol esters of little significance in differentiating obstructive from parenchymatous jaundice. This is easy to understand, since biliary tract disease is frequently associated with liver damage. The rise in the cholesterol ester fraction closely parallels the clinical improvement of the patient and occurs long before results of the oral hippuric acid test return toward normal. The ester fraction is of definite value in determining operative risk; with a cholesterol ester value of 60 mg. per hundred cubic centimeters or less, Greene and associates[16] found the mortality rate to be definitely increased.

A rapid decrease in the percentage of cholesterol esters, if the patient is not known to have an acute overwhelming disease of the liver parenchyma, such as acute yellow atrophy, may signify obstructive jaundice. Therefore, surgical intervention may be deemed a wise procedure for possible stone in the common duct when other indications may be lacking for this procedure.

The reduction of cholesterol esters in liver disease is probably the result of decreased ability of the liver cells to synthesize cholesterol esters or to release them to the blood.[60]

Fat Absorption.—Sullivan and Fershtand[55] studied fat absorption curves following the ingestion of 100 Gm. of cottonseed oil. Their observations were made on 43 normal young men and 10 patients with hepatic disease. The average value for total serum lipoids in the fasting state determined by the Ruckert volumetric lipokrit method for 43 healthy young men was 0.576 cubic centimeter per hundred cubic centimeters. Body weight and diet apparently had no effect on the level of the total lipoids during fasting.

In this normal group the average rise was +30 per cent at the end of the third hour post prandium and +65 per cent at the end of the sixth hour; however, at the end of the ninth hour the lipoids had fallen practically to the fasting level of 5 per cent. The height of absorption was between the third and the sixth hour, and absorption ceased shortly after the sixth hour. In a group of patients with definite evidence of liver disease the absorption at the end of the third, sixth and ninth hours was 8.9 per cent, 16.9 per cent and 22.5 per cent, respectively. The fat absorption curve for patients with definite evidence of disease of the liver apparently denotes the diminished and delayed absorption of ingested food and is sufficiently characteristic and different to be of aid in determining the status of the function of the liver.

Protein Metabolism

Plasma Proteins.—The liver stores protein and is the principal site of origin of the plasma proteins. During liver disease these activities are disturbed, and changes in the plasma proteins are often noted. Severe liver damage has long been known to be associated with hypoproteinemia, characterized by low serum albumin and normal or increased serum globulin. These changes in the plasma proteins, however, have not been marked except in the presence of severe liver damage.

There is some difference of opinion regarding the clinical significance of these changes. However, recent studies on patients with cirrhosis of the liver have shown that the total plasma protein value was decreased, and particularly the albumin fraction. I have found that in cirrhosis of the liver and other hepatic diseases the albumin-globulin ratio approaches 1:1. However, this is not evident as a rule without corresponding clinical manifestations of liver disease. I have found that other evidence obtained from liver functional tests usually parallels the change in the albumin-globulin ratio. It is necessary to rule out other causes of disturbance in the albumin-globulin ratio, particularly in cases of nephrosis and severe alkalosis and even in some cases of marked hypothyroidism. In addition to the quantitative changes, recent immunologic studies of the proteins in hepatic disease tend to confirm the assumption that the mixtures of proteins which make up the so-called albumin and globulin fractions might be altered in some of their physical and chemical properties.

Most investigators feel that the decreased levels of serum protein in instances of hepatic injury probably result from the failure of protein or the protein-building substances of the liver, in addition to the alteration of the equilibrium between the circulating and the stored protein. In patients with ascites the loss of albumin in the ascitic fluid or the increased capillary permeability, allowing the escape of protein into the tissues, may be a primary factor in the reduction of the amount of albumin in the serum. Further study of this problem reveals that the colloid osmotic pressure of the blood serum has been markedly lowered in the presence of hepatic disease. This has been further corroborated by producing experimental hepatic damage in animals and observing their similar decreases in pressure. Further, even in cases of cirrhosis of the liver with ascites when the serum protein was normal, the colloidal osmotic pressure was reduced.

Butt and his associates[7] reported that in a few cases of cirrhosis of the liver they found the colloid osmotic pressure of the blood serum to be as low as one-third of the normal value. They also found that for patients with obstructive jaundice the values for the colloid osmotic pressure were substantially reduced without respect to the depth of jaundice in individual cases, and they finally concluded that for all types of conditions studied there is no constant relation between the level of serum protein and the colloid osmotic pressure. There was, as might be predicted, a better correlation between the osmotic pressure and the concentration of serum albumin. In hepatic disease no constant "edema level," as measured by the colloid osmotic pressure, could be demonstrated.

Recently electrophoretic analyses of the plasma proteins in cases of liver disease of varied degree and type have shown that plasma protein changes occur early in liver disease when the usual chemical precipitation methods show few or no changes.[14]

Normal human serum protein is shown by electrophoresis to consist of albumin (including prothrombin), and alpha, beta and gamma globulin. Gray and Barron[14] found an abnormality of the concentrations of two or more of these protein fractions in every case of liver disease they studied. Most marked and most frequent were the increases in gamma globulin and the impaired production of the smallest molecular weight fraction, the albumin. The serum protein changes seemed to be caused mainly by inability of the liver to produce normal serum protein, especially the albumin fraction, and the more severe this decrease in albumin production, the greater was the compensatory increased production of gamma and, to a lesser extent, beta globulins. This production of the proteins of higher molecular weight seems to be easier for the damaged liver and may be the cause for the hyperproteinemia that is frequent with chronic liver disease. The serum protein changes were most marked with cirrhosis, less prominent with acute parenchymatous hepatitis and least prominent with metastatic carcinoma of the liver.

Aminoacid Tolerance Test.—The aminoacid tolerance test by the old technics was of little value in early liver disease. Lyttle and his associates,[29] however, devised what they called a more promising test. They injected intravenously 2 cubic centimeters of casein hydrolysate, diluted with an equal volume of 5 per cent dextrose in saline, per kilogram of body weight and took blood samples before and at five, fifteen, thirty-five and ninety-five minutes after injection. The plasma aminoacid nitrogen was determined by the gasometric ninhydrin method of Van Slyke and associates. In the control patients the preinjection level was always reached by ninety-five minutes, and there was considerable retention at thirty-five minutes. It is thought that a significant delay in the clearance of injected aminoacids occurs with liver disease. Lyttle and associates[29] could not correlate this tolerance test with other liver function tests and suggested that the various functions of the liver are selectively impaired.

Tyrosine Metabolism.—The demonstration of tyrosinuria is diagnostic rather than indicative of liver function; it is a sign of an autolytic process in the liver. Tyrosine may be demonstrated by the recovery of tyrosine crystals, a difficult and tedious process; by a positive reaction to Millon's reagent, a nonspecific reaction necessarily attended by errors, or by the tyrosinase method, which is the most specific. With acute yellow atrophy, continued extreme tyrosinuria is present and is pathognomonic. Other autolyzing lesions result in intermittent or less intense tyrosinuria.

Jankelson and associates[24] found tyrosinemia to be frequent with liver disease and to serve as an index to the severity of the damage. Bernhart and Schneider[6] developed a tyrosine tolerance test which they found sensitive for liver damage. Its value has not yet been established.

Functions Dependent on Integrity of Serum Colloids and Electrolytes

The Colloidal Gold Reaction of Blood Serum as an Index of Liver Disease.—Recently Gray,[15] working at the University of Chicago, made a splendid contribution in reporting certain studies of the colloidal gold reaction of the blood serum in liver disease. These studies of the colloidal gold reaction of the blood serum in hepatic disease were instigated by the observation that alteration in the plasma proteins, particularly in the euglobulin fraction, is frequently associated with liver disease and by the fact that the euglobulin fraction has been shown to play an important role in colloidal gold precipitation. The colloidal gold reaction of the blood serum was studied in 46 cases of hepatic cirrhosis and in 14 cases of acute parenchymatous disease of the liver; the diagnosis was confirmed by autopsy or biopsy in 11 instances of the first group and in 2 of the second. Similar studies were undertaken in 25 cases of neoplastic involvement of the liver and in 11 cases of miscellaneous hepatic disease; the diagnosis was confirmed in 13 cases of the former group and in 8 of the latter by autopsy, biopsy or laparotomy. Twenty syphilitis patients without clinical evidence of liver disease were studied likewise. The control series consisted of 95 patients, of whom 20 were normal adults and 75 had various extrahepatic diseases. Of the latter group, normal livers were found in 22 by autopsy, biopsy or laparotomy.

TABLE 6.—INCIDENCE OF POSITIVE SERUM COLLOIDAL GOLD REACTIONS IN LIVER DISEASE

	Patients with:					
	Cirrhosis of the liver	Acute parenchymatous liver disease	Neoplastic involvement of the liver	Miscellaneous hepatic disease	Extrahepatic diseases	Normal adults
Persons studied	46	14	25	11	75	20
Autopsy, biopsy or laparotomy	11	2	13	8	22	
Pos. colloidal gold reaction	46	13	19	11	2	0
Neg. colloidal gold reaction	0	1	6	0	73	20
Takata-Ara reaction	28/35	3/8	2/12	⅓ Total	34/58—58.6%	

Total number of patients with liver disease studied	96
Positive serum colloidal gold reactions	89
Percentage positive reactions	92.7
Patients with no clinically demonstrable liver disease	95
Negative serum colloidal gold reactions	93
Percentage of negative reactions	97.9

Method.—Two cubic centimeters of venous blood is obtained from the patient before breakfast and centrifuged. One-tenth of a cubic centimeter of clear serum is removed and diluted to 1:350 with 0.9 per cent sodium chloride. In the first of a series of 10 tubes is placed 1.8 cubic centimeters of 0.3 per cent sodium chloride. In each of the following 9 tubes is placed 0.1 cubic centimeter of 0.3 per cent sodium chloride. Then 0.2 cubic centimeter of the serum, previously diluted to 1:350 with 0.9 per cent sodium chloride, is placed in the first tube of the series. This is mixed, and 1 cubic centimeter of the mixed contents is transferred to the second tube and mixed. One cubic centimeter is transferred throughout the series of 10 tubes in this manner, and 1 cubic centimeter is removed from the last tube and discarded. Five cubic centimeters of colloidal gold, properly acidified, is added to each tube, and the tubes are read in twelve to twenty-four hours.

Care was taken to keep the *p*H of the colloidal gold about 7.12. The results were tabulated as a regular Lange reaction:

Red	0	Blue	3
Red blue	1	Light blue	4
Orchid	2	Colorless	5

Any reading that starts with a number below 5 is negative; otherwise the result is positive.

These studies indicate the high incidence of positive serum colloidal gold reactions in liver disease. The colloidal gold reaction was positive in 89 of the 96 cases of hepatic disease studied (92.7 per cent). The test is considerably more sensitive than most other tests for liver damage. Mateer and associates[34] confirmed this marked sensitivity, but they concluded that the test is not suited to routine hospital use because of the necessity of determining the amount of hydrochloric acid needed for preparing the colloidal gold solution. This is done by adding various amounts of acid to 50 cubic centimeter volumes of gold solution and testing against known positive and negative serums to find the optimum amount of acid. Then the final solution is tested against 10 to 20 normal serums to make certain that no false positive reactions occur. The solution must be made up at least every six weeks. Despite these laborious laboratory procedures, Mateer and associates[34] found 10 per cent false positive results on normal serums unless the colloidal gold solution was restandardized (as to amount of acid needed) with 10 to 20 normal serums every two weeks.

Recently Gray[15] found by electrophoresis studies that an increase in the serum gamma globulin and a decrease in the serum albumin are the causes of the precipitation of the gold.

Cephalin-Cholesterol Flocculation Test.—During the course of some immunologic studies Hanger[18] noticed that cephalin-cholesterol suspensions were flocculated by serum from patients with liver disease. The mechanism of the flocculation is still unknown, but there seems to be a change in the globulin fraction in the abnormal serum that changes the surface potential of the colloids of the cephalin-cholesterol mixture and causes flocculation. No correlation was found with the albumin-globulin ratio, the serum bilirubin, phosphatase or cholesterol levels, the Wassermann test, sedimentation rate, formolgel reaction or Takata-Ara test. Hanger[18] suggested that flocculation reflects active disease or irritation of the liver cells and is not a test of what the liver can do.

The test has been found to an extremely sensitive indicator of liver disease. It is simple, but the interpretation is easily vitiated by technical errors.

Technic.—One hundred milligrams of cephalin obtained from fresh sheep brain is mixed with 300 mg. of cholesterol in 8 cubic centimeters of Squibb's anesthesia ether. One cubic centimeter of this stock ether solution is added drop-wise and with stirring to 35 cubic centimeters of fresh, triply distilled water at a temperature of 65 to 70 C. The mixture is then heated slowly to boiling and allowed to simmer until the final volume is reduced to 30 cubic centimeters.

After the mixture has cooled to room temperature, 1 cubic centimeter is added to a centrifuge tube containing 4 cubic centimeters of 0.85 per cent saline and 0.2 cubic centimeters of the patient's serum. The tube is thoroughly shaken, stoppered with cotton and allowed to stand in a quiet place. Readings are made at twenty-four and forty-eight hours, the reactions being graded from 0 to 4 plus with respect to the degree of flocculation. Control tubes without serum and with known positive serum respectively are useful.

All the glassware used must be washed carefully, to avoid traces of heavy metals. False positive reactions may result from damage to the serum by unusual cold or warmth or by heavy bacterial contamination. The serum should be used within six hours after the blood is drawn.[37]

Certain diseases give high percentages of false positive reactions, of which some may be caused by concomitant hepatic disease. Among these are subacute bacterial endocarditis, "virus" pneumonia, disseminated lupus erythmatosus, infectious mononucleosis, rheumatoid arthritis and therapeutic malaria. The test may be negative with rapidly subsiding hepatitis when jaundice is still present and with extensive cirrhosis or carcinoma when the hepatic lesion is not in an active phase.[18]

Despite careful attention, there have been striking differences in the reports of different workers with respect to false positive reactions. These differences seem to be caused by great variations in the sensitivity of different batches of cephalin. Rosenberg and Soskin[40] suggested allowing the cephalin to stand exposed to the air for about six weeks to eliminate false positive reactions. Mateer and associates,[34] on the other hand, found that while fresh cephalin is too insensitive, cephalin aged in the sun in unstoppered bottles for several weeks yields false positive results on normal serum. They suggested the use of cephalin that has been ripened in the ice-box for four or five months or aged in the sun. It is evident that each batch of cephalin must be assayed on known serums. It is safest in general to disregard flocculation of less than 2 plus.

In his original description Hanger suggested that a positive reaction depends on changes in the fibrinogen fraction produced by a diseased liver. In his most recent article,[25] however, he expressed doubt of his hypothesis, since the flocculating activity of serum in both the colloidal gold and cephalin flocculation tests was found to be associated with the gamma globulin fraction, whether derived from normal or pathologic serum. Colloidal gold flocculation by gamma globulin was inhibited by addition of an electrophoretically separated albumin fraction of the serum proteins, but a difference in the inhibiting power of different preparations of albumin suggests that a substance that migrates with the albumin fraction is responsible. Cephalin flocculation is not inhibited by addition of the albumin fraction to the gamma globulin.

The Takata-Ara Test.—The Takata-Ara test presupposes that in hepatic disease there is a diminution of the colloid protective action in the blood serum owing to an increase in the globulin content. This test is based on the fact that when blood serum or ascitic fluid is treated with 0.5 per cent mercuric chloride, a pearly flocculum results, and occasionally a reddish precipitate occurs. The latter, however, is not considered a specific reaction.

Technic.—The test is performed within one to two hours after the blood is drawn. One cubic centimeter of 0.9 per cent solution of sodium chloride is placed in each of 6 small tubes. To the first tube 1 cubic centimeter of serum is added. After the serum has mixed with the saline solution, 1 cubic centimeter of the mixture is added to the saline solution in the second tube. This procedure is continued with each of the 6 tubes; 1 cubic centimeter of the mixture from the sixth tube is discarded. The tubes contain serum dilutions of 1:2 to 1:64. Twenty-five cubic centimeters of 10 per cent sodium carbonate is added to each tube. After each tube is shaken, 0.15 cubic centimeters of 0.5 per cent mercuric chloride is added. The tubes are thoroughly shaken and are examined after five minutes and again after twenty-four hours. A positive reaction is indicated by a pearly flocculum. A strong positive reaction is denoted by a definite flocculation in 4 or more tubes or in 3 tubes, at least one of which shows a flocculum occupying about one-third of the column. A positive reaction is indicated by a definite but slight flocculation in 3 or 4 tubes. A weak positive reaction presents a definite but minimal flocculation in no more than 3 tubes. A minimal flocculation in 1 or 2 tubes is regarded as a negative reaction.

The results of this test, while at first thought to be more or less specific for the diagnosis of atrophic cirrhosis of the liver, are extremely variable. Chasnoff and Solomon[9] found negative reactions for cirrhosis of the liver while patients showed evidence of advanced hepatic cirrhosis. Furthermore, by the time the test becomes positive, clinical evidence is so overwhelming that one does not need to resort to a test tube reaction for a diagnosis. The test is empiric, not specific for either injury of the liver or cirrhosis. However, in the presence of some hepatic disease, a positive Takata-Ara reaction is more likely to indicate cirrhosis than any other.

Excretory Functions

Bilirubin Clearance Test.—This test measures the ability of the liver to remove injected bilirubin from the blood. The injected bilirubin is all excreted in the bile and is not stored by the reticuloendothelial cells except possibly in complete obstructive jaundice. Weech and associates[59] pointed out that the rate of excretion is affected by the basal plasma bilirubin level. They assumed that the blood level of bilirubin depends on an equilibrium between the rates of formation and of excretion, and that the rate of excretion is proportional to the square of the concentration in the blood; with these assumptions they were able to adapt the bilirubin clearance test for use in hyperbilirubinemia.

There is a great reserve of the liver's ability to excrete bilirubin, but the test has been shown to be one of the most sensitive for detecting early liver damage. One of the principal objections to the test is the expense of the bilirubin.

Technic.—The bilirubin for injection is dissolved in about 15 cubic centimeters of 1:10,000 sodium carbonate that has been brought to the boiling point and allowed to cool to 80 C. The patient must be without jaundice and under basal conditions. A blood sample is taken, and 1.0 mg. of bilirubin per kilogram of body weight is injected intravenously. A second blood sample is obtained four hours after the injection. Blood bilirubin is determined by the photoelectrometric method of Malloy and Evelyn[32] or by comparison with standards of potassium dichromate.

A retention of more than 5 per cent of the injected bilirubin after four hours on this dose indicates liver damage. If 1.5 mg. per kilogram is the dose used, a retention of up to 15 per cent after four hours may be normal.

In the presence of hyperbilirubinemia, Weech and associates[59] used a dose of 5 mg. per kilogram of body weight. They evaluated the bilirubin clearance as the velocity constant of excretion by means of the formula:

$$K = \frac{1.513}{Leq\ (t_2 - t_1)} \log \frac{(L_2 + Leq)\ (L_1 - Leq)}{(L_2 - Leq)\ (L_1 + Leq)}$$

K = velocity constant of excretion
t = time in minutes after injection
Leq = bilirubin level of blood before injection
L_1 = bilirubin level of blood at t^1 (five to seven minutes after injection)
L_2 = bilirubin level of blood at t^2 (two to four hours after injection)
When K—2.5 $\times 10^{-3}$, liver function is normal.
When $K = 2$ to 2.5×10^{-3}, damage is presumptive, and a value below 2×10^{-3} indicates positive damage.

The Azorubin S Test.—Azorubin S, a dark red, stable, water-soluble dyestuff of the mono-azo group, was first introduced as an indicator of hepatic function by Tada and Nakashima[56] in 1924. They injected it intravenously and by duodenal intubation observed the color changes in the bile. In normal subjects as much as 95 per cent of the dye was excreted in the bile, the remainder being eliminated in the urine. Thus renal disturbances can exert only a negligible influence on its excretion by the liver. A delay in appearance of the dye in the bile or a prolonged urinary excretion was regarded as of pathologic significance. The dye was found to be harmless and devoid of untoward effects and when compared with 62 other dyes yielded the most reliable results (bromsulfalein was not included in their study).

Fenstermann,[12] in 1926, observed a close parallelism between the extent of liver damage and impairment in the hepatic excretion of azorubin S. Weiss,[61] in 1935, in his studies found azorubin S preferable to bromsulfalein. Eppinger,[11] in 1937, corroborated the findings of the earlier investigators and extolled the virtue of the azorubin S test. He stated that it is of greatest value in the differentiation of "catarrhal" from parenchymatous jaundice, the presence of bile-stained duodenal contents in the absence of biliary dye indicating the latter form. In some cases of suspected liver damage without icterus the azorubin S test was unique in its detection of impaired function.

Method.—After an over-night fast, a narrow flexible tube is passed into the duodenum and its position confirmed fluoroscopically. When bile begins to flow through the tube, 4 cubic centimeters of a sterile 1 per cent aqueous solution of azorubin S is injected intravenously. Five minutes later, 40 cubic centimeters of 25 per cent aqueous magnesium sulfate solution is administered through the duodenal tube. The duodenal contents are collected in separate test tubes at one to two minute intervals, and the time elapsing between the injection of the dye and the appearance of a very deep red efflux is designated as the "appearance time." The dye normally appears in the bile in eight to twenty-five minutes, and a deep cherry-red color occurs in fifteen to thirty minutes. For color determinations and comparisons, the best results are obtained by observing the solutions in bright daylight; slanting the tube against a white background is also helpful.

Using a colorimetric method, Zinny,[64] in 1926, measured the amount of dye excreted in the bile and found that an excretion of less than 0.01 Gm. in one hour is significant of liver damage. While perhaps more accurate, this method seems unnecessary. Fenstermann[12] expressed preference for a simple colorimetric examination of the urinary dye, but this procedure proved unreliable in my hands.

Rosenberg and Soskin,[41] utilizing this test and comparing its value with that of the bromsulfalein test, found that the detection of lesser degrees of hepatic insufficiency (chronic hepatitis) by the azorubin S test in the face of bromsulfalein failures (3 of 4 cases) is significant and expressed concurrence with the experience of Eppinger.[11] They also concluded that in cases of relatively early chronic hepatitis the azorubin S test is superior to the hippuric acid and the bromsulfalein test. However, since this test is dependent on duodenal intubation, the errors that accrue from it are similar to those of any other test which depends on this method of extraction from the patient.

The Rose Bengal Test.—The rose bengal test, similar to other dye tests, depends on the ability of the liver to remove the dye from the blood stream within a certain period. No attempt is made to calculate the amount of dye on the basis of body weight. Usually 10 cubic centimeters of a solution of rose bengal in triply distilled water is injected into the vein of an arm, and two minutes later blood is withdrawn from the vein of the opposite arm and used as a standard. A sample of blood is drawn eight minutes after the injection and compared with the standard. Normally 50 per cent or less of the injected dye is present in the blood after eight minutes. Retention of more is considered indicative of hepatic damage. The test gives results comparable to those obtained with bromsulfalein. The difficulties of this test are in obtaining a satisfactory standard and adequate mixing of the dye in the blood stream and the rigid time requirements.

Althausen and his associates[1] have used the spectroscopic method for determination of rose bengal, and in their work they found that in normal patients at the end of eight minutes 55 per cent of the dye was retained, and at the end of sixteen minutes, 35 per cent. Their reason for using the spectroscopic method is that the test can be carried out in the presence of jaundice, moderate hemolysis and lipemia.

The Bromsulfalein Test.—Of all the dye tests, this is probably the one most commonly used. Rosenthal and White's original method[42] consisted of the injection intravenously of 2 mg. per kilogram of body weight, and the estimation, by comparison with standards, of the amount of the dye in blood serum taken five minutes and thirty minutes later. (No dye should be left in the serum after thirty minutes if liver function is normal.) This test lacked sensitivity, and O'Leary, Greene and Rowntree[36] improved it by injecting 5 mg. of dye per kilogram of body weight. There has been some disagreement as to how much retention thirty minutes after this dose should be called normal. Helm and Machella[19] expressed the opinion that there should be no retention at thirty minutes; Israel and Reinhold[22] called retention of more than 6 per cent abnormal, and Rosenberg and Soskin[41] stated that a retention of less than 10 per cent is normal. Mateer and his associates[34] recently showed that use of these various criteria for normal causes a tremendous variation in the sensitivity of the test, and proposed a more reliable modification based on the serial method introduced by MacDonald.[30] That author found that an abnormal liver with some reserve can do in time all that a normal liver can do with respect to excretion of bromsulfalein, and suggested using the time for complete clearance of dye from the blood as the criterion of normal. With the 2 mg. dose, eighteen to twenty minutes was demonstrated to be a conservative estimate for normal clearance time. MacDonald[30] found that little more time is needed for removal of 5 mg. per kilogram than for removal of 2 mg. (normal clearance time of twenty-five minutes), but Mateer and associates[34] conclusively established the normal clearance time for the 5 mg. dose at forty-five minutes. This 5 mg., forty-five minute test was more sensitive than the 2 mg., twenty minute test and, when another estimation of dye retention at sixty minutes was added, afforded a reliable measure for the degree of liver damage.

Removal of the dye from the blood is thought to be in large part a function of the reticuloendothelial system, but it is obvious that the parenchymal liver cells are involved, since disease of those cells affects the clearance test markedly. Cantarow and Wirts[8] found that the rate of excretion of bromsulfalein in the bile may be more sensitive even than the rate of removal from the blood (old standards).

Clinically, the bromsulfalein test is useful in detecting mild or latent liver damage and estimating its degree, and it is of prognostic significance since marked impairment of clearance implies an unfavorable outcome. The value of the test is much impaired when hyperbilirubinemia is present.

Sodium Tetraiodophenolphthalein Test.—The Rosenthal-Rowntree test based on the assumption that the liver will secrete phenoltetrachlorphthalein has given rise to the use of sodium tetraiodophenolphthalein in a combined test of liver and gallbladder function. Intravenous injection of a solution of 2.5 Gm. of this salt is usually given and samples of blood taken one-half and one hour after injection. Normally patients excrete all but 15 per cent of the dye at the end of thirty minutes and all but 5 per cent at the end of sixty minutes. Graham and his co-workers[13] maintained that the retention of 12 per cent at the end of one hour may be a contraindication for surgical intervention and indicative of definite liver damage.

At the same time, one may be able to determine the entrance or lack of entrance of the dye into the gallbladder and whether the gallbladder may concentrate this dye and later evacuate it after the administration of a fat meal. The test should not be used in the presence of liver damage, of acute cholecystitis or of acute cystic duct obstruction with hydrops of the gallbladder. In addition, a fairly high retention may result in patients with chronic passive hyperemia of the liver associated with right ventricular heart failure.

According to Cutler[10] no constant relation has been discovered between the results of this test and the postoperative course in the cases observed.

Detoxication Functions

The Hippuric Acid Test.—This is a test of the ability of the liver to conjugate benzoic acid with glycine to form hippuric acid. Normally about 700 mg. of hippuric acid is excreted per day, and this excretion is increased by the intake of benzoates such as the salts or those in cranberries or plums. The rate of hippuric acid excretion depends chiefly on the ability of the liver to make glycine available, but also on its ability to conjugate glycine with benzoic acid and the ability of the kidneys to excrete hippuric acid in the urine. The ability of the liver to produce glycine seems to be affected early in liver disease; hence the test is a sensitive one. Probstein and Londe[38] demonstrated that some patients may show a decrease in hippuric acid output, caused mainly by a slowing of the conjugation mechanism rather than an impairment of the ability to make glycine available. Six of their 30 patients with low hippuric acid excretion showed slow conjugation.

The hippuric acid excretion test was first used as an index of kidney reserve rather than as a liver function test. Since it has been applied as a liver test it has been suggested that a urea clearance test be done at the same time to exclude abnormal results caused by inability to excrete hippuric acid normally. Schwei and Quick[43] showed that the rate of urinary excretion of hippuric acid is 50 per cent higher than the rate of synthesis and suggested that only severe renal disease need be considered a cause of lowered excretion. Machella and his associates,[31] however, have demonstrated a direct correlation between the hippuric acid excretion and the volume of urine excreted in the same period. Diuresis in a patient with liver disease may, therefore, increase a low to a normal value.

The test is subject to certain technical errors that may impair sensitivity or specificity. Probstein and Londe[38] expressed the opinion that the 6 Gm.

dose for the oral test is too large, after finding that 4 Gm. of sodium benzoate gave as high a conjugation rate as 6 Gm. They used an excretion of less than 50 per cent in the first hour as the criterion of abnormality. It has been found recently also that the addition of ammonium sulfate to the urine (0.5 Gm. per cubic centimeter) is necessary to precipitate the hippuric acid so that only 0.1 Gm. per hundred cubic centimeters remains in solution. If this salt and an excess of hydrochloric acid are not added, the determination of hippuric acid becomes inaccurate. For accurate work the hippuric acid is probably best determined chemically, since some of that found by the gravimetric method is due to benzoic acid in the precipitate.

An intravenous test[39] has been devised to eliminate inaccuracies and difficulties caused by gastrointestinal stasis and delayed absorption of the sodium benzoate. This test has also been found to be about 85 per cent more sensitive than the oral test.[34] In the oral test, 6 Gm. of sodium benzoate is administered in 30 cubic centimeters of water, followed by one-half glass of water. The patient voids immediately before ingestion and then hourly for four hours. In the intravenous test, 1.77 Gm. of sodium benzoate in 20 cubic centimeters of water is injected after the patient voids, and the urine is collected for the next hour. The urine samples are carefully measured, and the precipitate is obtained by addition of an excess of concentrated hydrochloric acid and 0.5 Gm. ammonium sulfate per cubic centimeter of urine. After thirty to sixty minutes the precipitate is filtered, washed with cold water and weight. To the weight of hippuric acid obtained per hundred cubic centimeters of urine is added 0.1 Gm., to allow for that which remains dissolved in the urine. To convert to benzoic acid, the value is multiplied by 0.68.

The lower limit of normal for the excretion by the oral test is 3.0 Gm. of sodium benzoate, and 1.5 Gm. or less constitutes a contraindication to surgical procedures. Some investigators have found that ambulant normal persons excrete more than bed-ridden normal persons. Little sensitivity is sacrificed in this test if all the urine voided for the four hours after ingestion of sodium benzoate is combined, and the test is much simplified by this procedure. By the intravenous test an excretion of less than 1.0 Gm. of hippuric acid during the first hour is abnormal.

Hypoexcretion is common with certain conditions not necessarily associated with liver damage. During normal pregnancy there is a progressive decrease in the formation of hippuric acid from the third month till delivery, with a rapid postpartum return to normal by about the eighth day.[46] This hypoexcretion may be a result of the increased volume of estrogen detoxication during pregnancy, leaving less glycine available for the formation of hippuric acid. Dehydration or vesical or renal obstruction to the urine flow may cause hypoexcretion, as do cardiac failure, malnutrition and many chronic diseases. These conditions may be associated with impaired liver function.

Rosenberg and Soskin[40] suggested that hyperexcretion (more than 115 per cent of normal) of hippuric acid may be caused by an irritation of liver cells in early liver disease. Hepler and Gurley[20] expressed the belief that there should be no upper limit and suggested that a large person with a large normal liver can excrete more hippuric acid; Machella and associates[31] explained hyperexcretion as a result of diuresis at the time of the test. The interpretation is thus in doubt.

The Cinchophen Oxidation Test.—This test is based on the estimation of the twenty-four hour excretion of oxycinchophen in the urine after the ingestion of a standard dose of 0.45 Gm. of cinchophen. In a group of 50 subjects without hepatic dysfunction, studied by Lichtman,[27] 30 to 100 mg., or 7 to 21 per cent, of the test dose was excreted as oxycinchophen. In patients with hepatic dysfunction, a high excretion of oxycinchophen follows the ingestion of a test dose. The increase in excretion of oxycinchophen in the urine may be useful as a qualitative index of an altered metabolism of the cells of the liver when they have lost their capacity to decompose this substance further.

The quantities of oxycinchophen excreted in the urine over twenty-four hours by 100 patients with hepatic dysfunction vary between 100 and 375 mg., or 21 and 78 per cent. In Lichtman's experience, morphine, codeine, cathartics and insulin tend to decrease the excretion of oxycinchophen; epinephrine, to increase the excretion. Marked impairment of renal function, high intestinal obstruction and malnutrition vitiate the results of this test.

Miscellaneous Functions

The Prothrombin Time Test.—The liver is the site of origin of prothrombin, so that liver disease is often associated with a disturbance of blood prothrombin. Early reports suggested a high degree of correlation between impairment in liver function and the degree of prothrombin deficiency. It was soon found, however, than an isolated test of prothrombin time is of little value as an index of liver function, although serial tests reflect the course of the disease fairly well.

The response to vitamin K therapy was suggested as a measure of liver function, and Andrus and Lord[2] recommended such a test as a reliable method of differentiating between obstructive and hepatogenous jaundice. The plasma prothrombin time is determined on two successive days by the Warner, Brinkhous and Smith[58] procedure, and if the levels are within 5 per cent of each other, 2 mg. of menadione is injected intramuscularly, and the prothrombin time is determined twenty-four, forty-eight and seventy-two hours later. The menadione is not injected until the levels on two successive days are within 5 per cent of each other, and the test cannot be done unless the initial prothrombin level is less than 80 per cent. With extrahepatic jaundice, there will then be a rise of 10 per cent or more after twenty-four hours or, failing this, a rise of 15 per cent or more after forty-eight or seventy-two hours. With hepatocellular disease the rise will not satisfy these criteria. An initial prothrombin time of more than 80 per cent is not found with hepatocellular disease.

Ziffren and his associates[63] pointed out that the two stage method of Warner, Brinkhous and Smith[58] must be used to determine the plasma prothrombin time if the test is to be used to indicate liver function. Authors who have used the simpler, one stage method have reported that the response to vitamin K is only a crude index of liver damage and that a normal response may be obtained even when severe damage is present.

Blood Phosphatase Activity.—Gutman and his associates[17] expressed the opinion that the Bodansky technic for determining the alkaline phosphatase activity of serum is of value in ruling out obstructive jaundice, since obstruction is an improbable cause of jaundice when the phosphatase activity is less than 10 Bodansky units. Various hepatotoxic agents may increase the phosphatase level to more than 10 Bodansky units, however, without the presence of obstruction to the bile tracts. Sharnoff and coworkers[44] found the phosphatase level to be unreliable in the differentiation of hepatocellular from obstructive jaundice. The mechanism of the changes in serum phosphatase values is unknown. Bone diseases also change the blood phosphatase values, independently of liver activity.

Serum Choline-Esterase Activity.—The serum esterase activity is measured by the liberation of carbon dioxide on addition of acetylcholine to serum and Ringer's solution. With liver damage there is, for some reason, a lowered serum choline-esterase activity. Many extrahepatic diseases also, however, are associated with lowered serum choline-esterase activity, and the test is not specific for liver disease.

Coproporphyrin Excretion.—Coproporphyrin I and III are the excretion products of protoporphyrin I (a useless by-product arising during hematopoiesis) and protoporphyrin III (the prosthetic group of hemoglobin, myoglobin, etc.). It has been found[28] that in liver disease the normal ratio of urinary to fecal coproporphyrin is increased in approximate proportion to the degree of liver damage and in obstructive jaundice parallels the degree of obstruction of the biliary ducts. This is the result of an increased urinary excretion and a decreased fecal excretion of coproporphyrin.[35] During the phase of acute hepatic insufficiency there are a decrease of urine output and a concomitant decrease in the urinary output of coproporphyrin. The significance of these findings remains to be worked out.

The Widal Hemoclastic Shock.—The Widal hemoclastic shock has been used in the past as a test for liver damage, on the basis that normally after a meal leukocytosis develops. Failure of this leukocytosis to develop has been suggested as indicative of liver damage. The so-called leukopenic index, which may be indicative of an allergic response of sensitized persons to various offending antigens, is a similar phenomenon. Therefore, a patient's liver may be relatively normal, and yet he may show a definite decrease in his leukocyte count after the ingestion of food to which he may be sensitized. Thus it is evident that this test is not as important as was formerly thought.

Conclusion

Numerous tests for the function of the liver have been devised. No one test seems to satisfy all the requirements at the present time. However, in the approach to the diagnosis of liver disease, any or all of them should be used. No one functional test is of absolute diagnistic value, and all of them are of a contributory nature. Too much reliance should not be placed on the significance of any one individual test, and in this field clinical judgment based on long-continued clinical experience assumes a major role.

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JAUNDICE

When bile pigment is present in excessive amounts in the blood (hyperbilirubinemia), it escapes into the tissues, namely, skin, mucous membranes and conjunctiva, which then take on a yellow tint. This condition is termed jaundice, or icterus. The bilirubin may appear in the urine but does not pass into the saliva or milk, or, as a rule, into the cerebrospinal fluid, except with prolonged bilirubinemia. Jaundice may be due to the production of bile pigment in excess of the amount with which the excretory power of the normal liver can cope, or it may result from the failure of a damaged liver to excrete bilirubin produced in normal amounts. In either case bile pigment accumulates in the blood and, when it reaches a certain degree of concentration, diffuses into the tissues to give the characteristic discoloration.

Jaundice, it must be emphasized, includes only conditions in which the concentration of the bile pigments in the blood is increased. Certain cases of yellowish discoloration of the blood and tissues are caused by accumulation of pigments other than bile pigments. Among these are carotenoids, hematin, xanthorubin and various lipochromes. Jaundice associated with an increase of blood hematin is of especial interest, since increases in bile pigment and hematin frequently follow the same type of lesion. The discoloration resulting from hyperhematinemia resembles that of ordinary jaundice except that it is more bronzed. It is probable that blood hematin is increased by an augmented rate of liberation of hematin to the blood and an impaired ability to dispose of it. Massive hematomas may release large amounts from hemoglobin without an accumulation of bilirubin, when "jaundice" and an elevated icterus index will be associated with a normal serum bilirubin level. Increases in hematin in the blood are noted with especial frequency in the jaundice resulting from pernicious anemia or malaria and in that associated with infection by pneumococci or the gas gangrene bacilli. A decreased ability of the liver to dispose of hematin in these conditions is probably responsible for some of the hyperhematinemia.

In order to understand the etiologic factors concerned, it is necessary to review the formation of bilirubin. Bilirubin is a derivative of hemoglobin liberated from broken-down red blood cells. This liberation takes place in the reticuloendothelial system in various parts of the body, *viz.*, the spleen, lymph glands, bone marrow and the general connective tissues, as well as the liver, and these tissues are responsible for the extrahepatic formation of bile pigment.

A certain amount of bilirubin is normally present in human serum. Usually this is said to be from 0.1 to 0.5 mg. per hundred cubic centimeters, but Johnson and Bockus[14] found that more than this is frequently encountered by the usual methods. This is due to the technical difficulties and errors of the test, or occasionally to hyperbilirubinemia unassociated with hematologic or hepatic disease. There is no evidence that the true secretory cells of the liver play any part in the formation of bilirubin. They merely excrete the pigment that reaches them preformed. This excretion takes place through the polygonal cells, passes into the bile capillaries, later into the bile ducts and finally into the hepatic ducts for excretion into the intestinal tract in the usual manner. It is interesting to note that the bilirubin which is found in the bile capillaries and bile ducts is different from that found in the blood stream. This difference is due to the fact that bilirubin does not exist *per se* in the blood, but is associated with the protein molecule or radical. The dissociation of this protein radical takes place in the liver cells.

On the basis of this dissociation the van den Bergh test was devised. Van den Bergh and Müller in 1916 demonstrated that bilirubin in the blood exists in two forms, shown by a difference in response to the Ehrlich reagent.

Solution A:	
Sulfanilic acid	0.1 Gm.
Concentrated hydrochloric acid	1.5 cc.
Water, up to	100 cc.
Solution B:	
Sodium nitrite	0.5 Gm.
Water	100 cc.

To perform the test, 10 cubic centimeters of solution A and 0.3 cubic centimeters of solution B are freshly mixed. This mixture is used as the reagent in both forms of the test.

The direct reaction is that which follows the addition of 1 cubic centimeter of the reagent to 1 cubic centimeter of serum. It may occur in one of three forms: (*a*) immediate, or prompt, in which a violet color due to the formation of diazobilirubin develops in from twenty to thirty seconds; (*b*) delayed, in which no change appears until a minute or more has elapsed, then a reddish color develops and gradually deepens to violet, or (*c*) biphasic, in which a red color appears promptly as in (*a*) but takes a variable length of time to change to violet.

The indirect reaction is obtained as follows: 1 cubic centimeter of serum is mixed with 2 cubic centimeters of 95 per cent alcohol. After this is shaken and centrifuged, to 1 cubic centimeter of the supernatant fluid, 0.25 cubic centimeter of the reagent mixture and 0.5 cubic centimeter of alcohol are added. A reddish violet color develops almost immediately.

One type of bilirubin gives the direct reaction; the other form gives the indirect reaction. A biphasic reaction, in which the color appears within thirty seconds but does not reach its maximum intensity for a variable length of time, is said to depend on a mixture of the two types of bilirubin. This interpretation of the van den Bergh reaction has been questioned by Cantarow and his group, who found that the direct reaction depends on neither the concentration of the direct-reacting bilirubin nor the proportion it forms of the total bilirubin, but on other undetermined factors.

According to the usual view, the blood bilirubin is practically entirely of the indirect-reacting type, and no bilirubin should be found in the urine. This theory assumes that indirect-reacting bilirubin cannot pass through the renal filter, but that the direct-reacting type can do so after it reaches a threshold of about 2 mg. per hundred cubic centimeters. This theory has been useful clinically, but enough experimental evidence has accumulated to necessitate its modification. Among this evidence are the occasional appearance of bilirubin in the urine when the bilirubin level of the blood is normal; the fact that there is still some question as to whether direct-reacting bilirubin acts as a threshold substance, and the fact that there is a considerable amount of direct-reacting bilirubin in normal serum.

Among the outstanding differences in the properties of the indirect-reacting and the direct-reacting bilirubin are the greater ease of oxidation of the direct-reacting type, its lesser solubility in chloroform and the fact that it dialyzes the more easily through a collodion membrane. It is probable that the indirect-reacting bilirubin is bound with a colloidal constituent of the blood plasma, while the direct-reacting bilirubin is in the free state. When substances of low surface tension are added to the blood, they break up the colloidal combination of the indirect-reacting bilirubin, and the blood serum then gives the direct reaction. Among substances of low surface tension that will have such an effect are bile acids, cholesterol and various lipoids, but there is no conclusive evidence that these are the substances responsible for the differences in the van den Bergh reaction in obstructive and in hemolytic jaundice.

Bilirubin liberated from the reticuloendothelial cells to the blood is in the indirect-reacting colloidal form, but it is changed by hepatic cells into the free form, and discharged into the biliary passages. From the hepatic cells or the biliary passages it may gain entrance into the blood and cause the blood serum to give a direct reaction to the Ehrlich reagent.

A consideration of the pathogenesis of the various possible types of hyperbilirubinemia leads to the classification of jaundice in several ways. Rich[28] differentiated a *retention jaundice,* caused by inability of the liver to take up all the bilirubin that reaches it so that some remains behind in the general circulation, and a *regurgitation jaundice,* caused by microscopic changes in the liver cells, which become unable to excrete the bilirubin into the bile canaliculi at a normal rate and excrete it instead into the lymph channels. McNee differentiated between *hemolytic jaundice,* which is caused by an over-production of bilirubin so that more is present in the blood than can be disposed of by the body, *obstructive jaundice,* caused by an obstruction in the biliary passages with an overflow of the bile into the lymph and blood, and *toxic, or infective, jaundice,* which is caused by damage to the hepatic cells, impairing their ability both to take up the bilirubin from the blood and to excrete it into the bile passages. These classes, are related as illustrated:

Retention jaundice	Hemolytic jaundice	
Regurgitation jaundice	Obstructive jaundice	Intrahepatic Extrahepatic
	Toxic, or infective, jaundice	Hepatocellular jaundice

It is useful to follow these classifications in the differentiation of possible causes of jaundice in a given case, but it must be recognized that there is probably no case of purely hemolytic, obstructive or hepatocellular jaundice. Hemolytic jaundice frequently is the result of the action of toxic factors that are disseminated throughout the body and that necessarily will affect the activities of the liver cells, impairing their functional capacity and making the hemolytic jaundice partially also hepatocellular. In the same way, simple obstruction of the biliary passages is followed rapidly by impairment of the function of the hepatic cells, and necrotic lesions in the conditions designated clinically as hepatocellular jaundice can cause some obstruction to the passage of bile down the biliary passages in proximity to the lesions.

Obstructive Jaundice.—In the obstructive (regurgitation) type, the bilirubin has been resorbed or regurgitated back into the vascular system either through a primary entrance by way of passage again through the cells of the liver into the hepatic veins or by means of absorption through the lymphatic vessels into the thoracic duct. Bloom, years ago, in experimental obstructive jaundice produced by ligating the common bile duct, showed that bilirubin appeared in the lymphatic vessels at the thoracic duct earlier that it appeared in the hepatic vein.

In obstructive jaundice an immediate van den Bergh reaction is indicative of the fact that the protein molecule has been dissociated from bilirubin, and therefore the bilirubin must have passed through the cells of the liver and been resorbed or regurgitated back into the blood stream. Anything that will obstruct the outflow of bile will prevent the normal entrance of bile into the intestinal tract and produce the clinical picture of obstructive jaundice. The obstruction may be extrahepatic, caused by stones in the common duct or parasites within its lumen, tumors at the head of the pancreas, chronic interstitial pancreatitis, enlarged lymph nodes pressing on the large bile ducts, a tumor passing on the common duct, ulcers or carcinomas of the ampulla of Vater, spasm of the sphincter of Oddi, stricture of the common bile duct, large pancreatic cysts distorting the common bile duct, metastatic nodes at the hilum of the liver or congenital obliteration of the ducts. Or it may be intrahepatic, by bile thrombi or swelling, tumors or necrosis of the liver cells, which occlude the bile capillaries and stop their function. Periportal cellular infiltration in hepatitis and serous hepatitis also may cause compression of biliary capillaries and intrahepatic biliary obstruction.

When the bile ducts are obstructed, the secretion of bile by the hepatic cells continues until the pressure in the ducts reaches 250 to 300 mm. of water. After that there is a suppression of biliary secretion, and the bile pigment probably is taken from the blood by the hepatic cells and excreted in to the hepatic veins and lymphatic vessels instead of into the bile capillaries. The bile that does find its way into the bile ducts before occlusion is slowly concentrated after occlusion of the ducts, and bile thrombi form and block the canaliculi. Many bile canaliculi also rupture under the excessive intraductal pressure, and any bile secreted into them leaks out into the hepatic parenchyma. The extruded bile causes degeneration of the hepatic cells that goes on to necrosis; the pressure also is detrimental to the hepatic cells. With the necrosis of cells, the cell cords of the lobules are disrupted, and the blood supply to many areas in the lobules is gradually reduced. Ascending infection from the duodenum may extend at this time and cause severe cholangitis. Early in the course of the obstruction, all but the most sensitive liver function tests will give normal results, but later, when the cholangitis and the necrosis begin to appear, the liver functions are all impaired, and it becomes more difficult to differentiate obstructive and hepatocellular jaundice with these tests, since both types are present.

Hepatocellular Jaundice.—Hepatocellular jaundice is caused by impairment in the ability of the liver to take bilirubin from the blood and to excrete it into the bile ducts. About 90 to 95 per cent of the liver must be removed before jaundice appears in animals, but clinically jaundice frequenty appears when there is little histologic evidence of damage to the hepatic cells. An explanation of this apparent discrepancy between the appearance of experimental and clinical hepatocellular jaundice may be found in the fact that the liver lobules obey an all-or-none law in their bilirubin function. It is probable that at any given time most of the liver's lobules are quiescent and that lobules alternate between periods of rest and activity in a fashion similar to that of muscle fibers. Hepatotoxins reduce the quantity of bilirubin that can be cleared from the blood and excreted by the lobules by damaging the lobules, and probably they also can prevent more lobules from entering into an active excretory phase, in that way causing jaundice even when the structural damage affects less than the expected 95 per cent of the total liver mass.

The causes of hepatocellular jaundice are classified (modified from Ottenberg and Spiegel[23]):

I. Infections causing degeneration of the liver and jaundice
    A. Infections in which hepatic degeneration is a dominant feature
        1. (*a*) Simple jaundice
            (*b*) Acute yellow atrophy
        2. Leptospirosis
        3. Yellow fever (*vide infra*, p. 375)
    B. General infections associated occasionally with jaundice
        1. Lobar pneumonia
        2. General septicemia
        3. Syphilis (*vide infra*, p. 399)
        4. Tuberculosis (*vide infra*, p. 399)
        5. Infectious mononucleosis
        6. Malaria (*vide infra*, p. 375)
        7. Oroya fever

II. Jaundice due to chemicals
    A. Direct injury to liver parenchyma
        1. Therapeutic agents: gold, chloroform, arsenic, ether, iodoform, avertin, etc.

  2. Accidental contacts: amanitotoxin, nitrobenzene, phosphorus, butins, etc.
  3. Industrial hazards: Tetrachlorethane, carbon disulfide, trinitrotoluene, etc.
  3. Experimental agents: Selenium, copper, etc.
- B. Primary hemolysis with secondary injury to live cells
  1. Therapeutic agents: phenylhydrazine, sulfonamides, incompatible blood tranfusion
  2. Accidental contacts: snake poison, bean poison
  3. Industrial hazards: arsine
  4. Experimental agents: distilled water, toluendiamine
- C. Idiosyncrasy, hypersusceptibility and allergic sensitivity
  1. Therapeutic agents: arsphenamine, cinchophen, liver extract, bismuth, sulfonamides, mercury

While it is thought that the damage is due primarily to changes in the liver cell, it is difficult to visualize how these changes could be entirely limited and not affect the smaller bile capillaries. If the liver cells is damaged, no matter what the cause may be, it is reasonable to suppose that the threshold for the excretion of bilirubin will necessarily be raised. Therefore it is to be expected that any condition which affects the liver cell will give rise to a bilirubinemia in which the blood stream has a large amount of normal serum bilirubin on one hand and a considerable amount of dissociated bilirubin on the other, owing to the resorption from the bile capillaries.

This combination of the two types of biliturin is classically found in cases of toxic and infective jaundice and gives rise to the so-called biphasic van den Bergh reaction. Toxic or infective jaundice may be caused by anything which damages the liver. It occurs most commonly with gallbladder disease with an ascending infection. It is seen with cirrhosis, no matter what the cause. It is present with febrile disturbances, owing either to cloudy swelling or to focal necrosis, depending on the cause of the fever. It may result from systemic or other infectious diseases. It is commonly seen with syphilis. It occurs in an epidemic form as in Weil's disease. It may be due to a chemical, a toxin or a poison, such as arsphenamine, phosphorus or chloroform. It may be present with thyrotoxicosis. It is classically seen as a component of right ventricular heart failure with resultant engorgement of the hepatic vessels. With all these conditions the indirect van den Bergh reaction far overshadows the direct.

Toxins, including both exogenous and endogenous poisons, act apparently by changing certain of the proteolytic enzymatic systems in the liver cells, with a resultant necrosis and fatty metamorphosis in those cells. Three major types of action that these toxins exhibit are cell injury by direct damage of the cell (characteristic of phosphorus, chloroform and carbon tetrachloride), by primary hemolysis of erythrocytes with secondary injury to the hepatic epithelium (characteristic of phenylhydrazine and hemolytic serum) and by idiosyncrasy and allergic reactions (characteristic of hepatic damage by arsphenamine and by the sulfonamides). Idiosyncrasy may be defined as an unusual, unexplained reaction to some substance. It implies the presence of an unusual type of cell metabolism that makes the cell display an increased sensitivity to the substance involved.

Exogenous Hepatotoxins.—Exogenous hepatotoxins may be classified as follows:

1. Those causing direct injury to the liver cells
   - A. Therapeutic agents: Gold, ether, chloroform, carbon tetrachloride, iodoform, avertin, tetraiodophenolphthalein, dinitrophenol, guanidine compounds (synthalin), acriflavine, arsenic
   - B. Accidental contacts: Carbon tetrachloride, arsenic, phosphorus, bean poison, amanitotoxin (mushrooms), nitrobenzene
   - C. Industrial hazards: Carbon tetrachloride, carbon disulfide, trinitrotoluene, tetrachlorethane, nitrobenzene, manganese
   - D. Experimental agents: Selenium and copper
2. Those causing hemolysis, with secondary damage to liver cells
   - A. Therapeutic agents: Phenylhydrazine, sulfonamides, incompatible blood (transfusion), trinitrophenol, hemolytic serums
   - B. Accidental contacts: Snake poisons, bean poison
   - C. Industrial hazards: Arsine
   - D. Experimental agents: Toluendiamine
3. Those causing manifestations of idiosyncrasy or an allergic reaction: Arsphenamine, sulfonamides, cinchophen, liver extract, bismuth, mercury

Certain of these substances merit individual consideration.

Chloroform.—There is much individual variation in the susceptibility of patients to liver damage by chloroform and allied substances, such as carbon tetrachloride, iodoform and ethyl chloride. The diet, the previous state of the liver and the treatment all affect the susceptibility. Fatty degeneration and necrosis, most marked in the area of the liver lobules surrounding the central veins may appear after anesthesia with chloroform, whose influence is counteracted by a preoperative diet high in carbohydrate and dairy protein, especially when fortified with choline and methionine. "Delayed liver damage" from chloroform is described frequently, because the symptoms of liver damage do not become apparent for several days. The sensitive liver function tests will show liver damage to be present, however, even during the supposed incubation period. Symptoms are vomiting, appearing one or two days after the anesthesia; jaundice, appearing shortly thereafter, and finally hepatic coma that may progress to death.

Carbon tetrachloride causes similar lesions and clinical manifestations after the patient has been exposed to a toxic concentration in industrial procedures or has used the drug as an antihelminthic agent. Careful preparation with a high carbohydrate diet should precede the use of this substance therapeutically. Treatment consists of the administration of a high carbohydrate diet, intravenous infusions of dextrose and judicious use of choline and methionine as soon as possible. Hepatic damage caused by ethyl chloride, avertin and related substances should be treated in a similar fashion. It should be recognized that after several exposures to the toxic action of these substances, fibrosis and liver damage become irreversible and toxic cirrhosis appears.

Phosphorus.—Phosphorus poisoning is not common, but it occurs occasionally. It results in extensive diffuse fatty changes of the liver, especially marked in the peripheral area of the lobules. The liver appears large, yellow and greasy on gross examination. Symptoms of hepatic insufficiency appear several days after the poisoning and progress to hepatic coma and frequently terminate in death. Vigorous treatment for hepatic failure is necessary to prevent a fatal outcome.

Mushrooms.—After poisoning caused by the ingestion of one of the mushrooms of the *Amanita phalloides* group, an extensive diffuse fatty degeneration of the liver resembling that caused by phosphorus poisoning frequently appears. Subacute yellow atrophy of the liver or cirrhosis frequently remains after recovery. During the active phase of the poisoning, liver symptoms are unusual; but after the acute poisoning has been overcome, jaundice develops gradually, and the liver is large and tender. Hepatic damage may progress to hepatic coma and death. Treatment is the same as for hepatic failure from any cause. Antitoxic serum for the amanitotoxin may be of use if it can be obtained early in the illness.

Eclampsia.—In the eclampsia of pregnancy the lesions of the liver are different from those of the acute yellow atrophy of pregnancy (*vide infra*, p. 401). In eclampsia the generalized toxemia brings about hemorrhagic necrotic lesions in the peripheral areas of the liver lobules, associated with thromboses in the branches of the portal vein. Other lesions include fatty changes in the hepatic cells and lymphocytic infiltration. Clinical manifestations of hepatic insufficiency, including jaundice and digestive and metabolic disturbances, are similar to those of hepatic insufficiency caused by other hepatotoxins.

Hyperthyroidism.—In hyperthyroidism, impairment of liver function occurs frequently as a result of nutritional deficiencies incident to the excessive metabolism. Fatty changes, necrosis, atrophy, fibrosis and regenerative changes appear in the parenchyma of the liver. Liver function tests show definite impairment in most cases. The depletion of the glycogen and the protein content of the liver cells in hyperthyroidism leads to increased susceptibility to liver damage. It is thought by some that in thyroid crisis, acute and severe liver failure is responsible for death. The susceptibility to liver damage and to hepatic insufficiency that results from hyperthyroidism makes careful preparation and intelligent study of the patient major factors in preoperative care. The principal measure to prevent the appearance of liver damage is the maintenance of proper nutrition despite the increased needs in this disease. Supplementing the diet with calories in the form of carbohydrate, with protein and with vitamins will be effective in preventing serious liver damage.

Hemolytic Jaundice.—Bile pigment (0.1 to 0.5 mg. per hundred cubic centimeters) is present in normal human serum. Any condition which increases red blood cell destruction also increases the formation of bile pigment. Unless the over-production of bile pigment is very great, the healthy liver, which possesses a large functional reserve, is able to meet the extra demand. When the disintegration of red cells is such that the balance between production and excretion of pigment cannot be maintained even by the normal liver, the bilirubin concentration in the blood rises above the normal limits.

A useful classification of the better known causes of hemolytic jaundice according to the mechanism of hemolysis (modified from Pepper[24]) follows:

1. Due to disease of the erythrocytes
    - Hemolytic icteroanemia
    - Sickle-cell anemia
    - Pernicious anemia
2. Due to parasitic destruction of erythrocytes
    - Malaria, Oroya fever

3. Due to allergic hemolysis
    - Favism
    - Drug idiosyncrasy, *e. g.*, to sulfonamides
4. Due to hemolysis by chemical agents
    - Exogenous: due to acetanilid, lead or snake venom
    - Endogenous: due to bile salts or altered plasma pH
5. Due to bacterial toxins
    - *Bacillus welchii*, pneumococci
    - Unidentified infections, as in some cases of acute hemolytic anemia
6. Due to specific hemolysis
    - Transfusions of incompatible blood
    - Erythroblastosis foetalis
    - Cold hemolysins, *e. g.*, cold in paroxysmal hemoglobinuria
7. Due to unknown mechanisms
    - Carcinomatosis
    - Cooley's anemia

It is because of the aforementioned factors that this type of jaundice frequently has been referred to as an extrahepatic form. Some authors have termed it "dissociated jaundice," because in this form, while there is an increase of serum bilirubin, there is no increase of bile acids. Since it is presumed that the bile acids are conjugated in the liver, it is not to be expected that their concentration in the blood will be raised in a purely hemolytic type of jaundice. However, it should be emphasized that in cases of severe liver damage bile acids may be absent from the blood, although hyperbilirubinemia is pronounced. In other instances of relatively mild hepatic insufficiency a converse type of "dissociated jaundice," namely, increased concentration of bile acids in the blood without icterus, is sometimes seen. This type may result also from increased destruction of hemoglobin in the presence of large hematomas or pulmonary infarcts.

Other Forms of Jaundice of Obscure Origin.—**Psychic Jaundice.**—Spasm of the bile ducts with resulting biliary stasis caused by psychic excitation, fright, worry or anger may cause jaundice of this type. The appearance of this condition may be sudden or delayed. Usually there are gastrointestinal disturbances, such as heaviness or pressure in the stomach and at times diarrhea. The best illustration of this type of jaundice is seen in the student who just before examination begins to show definite clinical manifestations of jaundice and in whom as soon as the fear disappears the jaundice rapidly recedes.

Allergic Jaundice.—Various foods that cause urticarial eruptions or angioneurotic edema have occasionally caused jaundice. The explanation of this phenomenon may be that the urticarial swellings or edemas cause turgescence in the region of the papilla of Vater or in the ducts themselves and thus produce jaundice by blockage. After the removal of the offending food or foods the jaundice usually disappears.

Inanition Jaundice.—This type is characterized by a slight yellow hue in the conjunctivas and the skin. It is supposed to be due to the relaxation of the bile ducts and the lowering of the blood pressure, permitting engorgement of the liver and resorption of the bile. It is found chiefly in cases of starvation, although well nourished persons at times may show a yellowish discoloration of the scleras.

Menstrual Jaundice.—The swelling of the mucous membranes of the bile ducts that occurs during menstruation is due to a congestion of the liver. After the menstrual flow appears, the jaundice disappears.

Pregnancy Jaundice.—Jaundice occurs at times during pregnancy, when it usually simulates the catarrhal type. Pressure of the enlarged uterus or constipation may be the cause. It usually subsides after delivery. However, occasionally acute yellow atrophy may be superimposed on the clinical picture.

Icterus Neonatorum.—Jaundice occurs in from 20 to 80 per cent of all otherwise normal newborn infants and is especially frequent after premature birth. It is thought that the destruction of superfluous fetal red cells after birth or placental destruction of maternal blood before birth causes the hyperbilirubinemia in icterus neonatorum. Davidson[6] has shown also that the liver does not assume the placental function of excreting bilirubin for some time after birth, and at least a part of the hyperbilirubinemia is caused by this lag, which may depend on the development of a balanced pulmonic circulatory system and closure of the ductus venosus to supply the liver with an optimum oxygen supply. This condition disappears spontaneously within a few days and must be differentiated from pathologic jaundice of the newborn, especially that caused by erythroblastosis foetalis, congenital anomalies of the bile ducts, congenital hemolytic anemia, cholangitis and sepsis.

Constitutional Hyperbilirubinemia.—Hyperbilirubinemia without hepatic or hematologic disease is not infrequent. This condition, also known as familial nonhemolytic jaundice, is thought by some to result from an elevation of the liver cells' threshold for bilirubin excretion without other cell damage. Kornberg[17] showed that the condition is characterized by a marked inability to excrete injected bilirubin, although other liver function tests give normal results. He also expressed the belief that the condition occurs more frequently than it is recognized.

Differential Diagnosis of Jaundice.—In the management of jaundice in any case, it is of major importance definitely to determine the nature of the disease as soon as possible, so that proper therapeutic measures can be instituted before damage becomes irreparable. A preliminary decision as to whether the case is one of obstructive jaundice best treated by operative measures or one of a "nonsurgical" type best treated medically is one of the first problems in the management also. Frequently both the nature of the causative lesion and the type of jaundice become apparent from a careful analysis of the history and physical examination. Laboratory tests are needed only to confirm the clinical impression and to follow the course of the disease in such cases. In other cases extensive laboratory tests will be necessary before one can decide whether surgical or medical measures are appropriate.

It is of some interest to consider the relative incidence of the different types of jaundice. An analysis of almost one thousand cases of jaundice showed that about one-half were of "medical" and the other half of "surgical" jaundice. In the medical group, one-fifth were of primarily hemolytic and the other four-fifths of hepatocellular type. The causes of jaundice in the surgical group were about equally divided between malignant and benign conditions.

Usually the diagnosis of the type of jaundice is simplified by first establishing the presence or absence of hemolytic jaundice. Frequently the history, physical examination and hematologic findings will be diagnostic of hemolytic jaundice. Such jaundice is generally only moderate or mild, and the tissues and skin are often less deeply stained than one might expect on the basis of the increase in the bilirubin concentration of the blood. The bilirubin accumulates because of production of more bilirubin than the liver can dispose of, and the blood serum gives the indirect van den Bergh reaction. Quantitative analysis of the blood for bilirubin will show a marked increase in the indirect-reacting bilirubin concentration but approximately normal amounts of direct-reacting bilirubin, unless an obstructive or hepatoxic element is added. The increased production of bile pigment leads to increased excretion of pigment in the bile and as a consequence to the appearance of greater quantities of urobilinogen and stercobilinogen in the stool. By quantitative methods one will find 300 to 2,000 mg. per day of these in the stool instead of the normal 40 to 280 mg. There will be no bilirubin and only normal amounts of urobilinogen in the urine. If complications occur and liver function is impaired (or possibly if more urobilinogen is resorbed from the intestine than even a normal liver can dispose of), some of the urobilinogen will not be utilized by the liver, and daily urinary output of urobilinogen will be increased.

Tests for Bilirubinemia.—The degree of bilirubinemia is measured in several ways. As mentioned before, the van den Bergh test is commonly used as either a qualitative or a quantitative test. A "unit" was defined by van den Bergh as 1 part of bilirubin in 200,000 parts of serum. Normal serum contains from 0.2 to 1 unit (*i. e.*, bilirubin is present in a dilution of 1 part in from 1,000,000 to 200,000 parts of serum, or from 0.1 to 0.5 mg. per hundred cubic centimeters). In the quantitative estimation of bilirubin in serum showing the direct reaction, the method has been rendered more accurate by the modification of Thannhauser and Anderson. This consists in adding first 0.5 cubic centimeter of the reagent to 1 cubic centimeter of the serum and a minute or two later 2.5 cubic centimeters of alcohol in 1 cubic centimeter of a saturated solution of ammonium sulfate. By adding the diazo reagent before the alcohol, the loss of bilirubin which results from its being carried down from the albuminous precipitate is avoided. When the alcohol is added later, the diazobilirubin compound is not precipitated but remains in the supernatant fluid. There is, nevertheless, a considerable error involved in the Thannhauser and Anderson method. Malloy and Evelyn[20] have developed a more accurate, photoelectric colorimetric method for the determination of serum bilirubin.

The quantitative van den Bergh test is of value in the detection of latent jaundice, *i. e.*, a hyperbilirubinemia which has not reached the level at which jaundice is clinically apparent, and is of further value in recording the progress of manifest jaundice.

A second indicator commonly used is the icterus index. This is dependent on comparing the color of the serum with that of a standard solution. A sample of blood is allowed to clot; after it is centrifuged, 5 cubic centimeters of serum is pipetted off and the color of the sample compared in a colorimeter with a 1:10,000 solution of potassium bichromate, which is defined as the color of serum with an icterus index of 1.

The colorimeter is set at 15 millimeters for the standard solution. This number is divided by the number on the serum scale at which the color of the serum and that of the standard solution match. The result is called the icterus index. Thus, if the reading of the serum scale is 3, the icterus index is 5. The normal icterus index is from 4 to 6.

To avoid the errors introduced by hemolysis or opalescence, the acetone modification is used. The serum is mixed with an equal volume of acetone, mixed and centrifuged, and the supernatant fluid is compared with the standards. An icterus index above 5 by this method is definitely abnormal.

Clinical Picture.—Patients with jaundice may have a very bizarre clinical picture, depending on the etiologic factors, the extent, the degree and the complications which may supervene. At the outset, if jaundice is not ushered in with a stormy clinical picture, patients complain, as a rule, of anorexia, ineptitude, malaise, headaches, slight nausea, flatulence, weakness and pruritus. The last may be the first symptom. These symptoms may appear before clinical evidence of jaundice, and later patients may complain of pain in the right upper quadrant of the abdomen, which may be due to changes in the liver capsule. Nausea may become more marked and be followed by vomiting. There may be chills and fever. The skin becomes discolored; perspiration stains the clothing yellow, and the urine becomes deeper in color. The most striking feature of the gastrointestinal system is the change in the color of the stools. Their clay color is produced by three factors: (*a*) the absence of bile; (*b*) the presence of undigested fat in quantities which may be increased from the normal 10 per cent to 55 per cent or more, and (*c*) the presence of bubbles of gas which result from the putrefaction caused by the intestinal indigestion.

If this condition is allowed to continue, the patient may become dull and apathetic, and in extreme cases cholemia supervenes. The pulse is slow unless there is an acute infective process present, and even then it is slower than it normally should be for the clinical picture. Physical examination of the abdomen may give entirely negative results, except for some enlargement of the liver. Tenderness may be elicited if there is an acutely stretched liver capsule or if there is an associated cholecystic disease. The spleen may or may not be palpable. Marked excoriations may be present on the body owing to scratching.

Any other physical findings present are usually associated with the disease causing the jaundice. There may be secondary anemia. The leukocycte level may be depressed or elevated.

The prothrombin time becomes greater than normal in a large proportion of jaundiced patients.

The coagulation time may be prolonged. The bleeding time is usually normal, unless there is some disturbance of the blood platelet–regulating mechanism or of the prothrombin metabolism. Hemorrhage or hemorrhages are not at all uncommon and may be severe. Cholemia, which may appear in patients with jaundice, is usually due to hepatic insufficiency. This subject will be discussed later in diseases of the liver.

In certain types of nonhemolytic jaundice (*e. g.*, familial nonhemolytic jaundice), the exact nature of which is unknown, and in some cases of hepatocellular jaundice, there will be an indirect van den Bergh reaction. The latter condition can be differentiated on the basis of impaired liver function, demonstrated by the hippuric acid test, the intravenous dextrose tolerance test, the decrease in the percentage of cholesterol esters in the blood and a positive reaction to the cephalin flocculation test.

Differentiation between obstructive and hepatocellular jaundice then becomes necessary. Often a history of repeated attacks of biliary colic or of exposure to hepatotoxins or the like leads one to the correct diagnosis with no difficulty. But colicky pains or pain in the right upper quadrant of the abdomen do not necessarily indicate gallbladder disease or biliary colic. In patients with acute atrophy of the liver due to poisoning and having marked jaundice, the fact that the liver capsule is stretched in the process of rapid regeneration accounts for the acute exacerbation of pain, just as it would account for the pain which occurs in acute right ventricular heart failure with extreme passive congestion of the liver and subsequent stretching of the liver capsule. Many patients have had surgical intervention for the clinical picture just described. Often the differentiation remains in doubt after a careful study of the history and examination, and differentiation by laboratory methods becomes more important.

If the icterus index continues to rise daily, it is indicative of an increasing process. However, it sooner or later reaches its fastigium. I have seen icterus indexes of 150 and 200 associated with toxic and infective jaundice. Daily variations in the icterus index are more suggestive of an intermittent obstruction than they are of toxic or infective hepatitis. No single test will make differentiation absolutely certain in all cases, and it is best to use several tests and to repeat them over a long period, in order to follow the course of the disease accurately. When jaundice has existed for more than six weeks the liver will be damaged, even when the jaundice started on a purely obstructive basis, and it is best then to treat the patient intensively for hepatocellular jaundice and later to perform an exploratory laparotomy. Cholecystography in such cases may aid in visualizing the biliary tract and any obstructive lesions that may be present, but failure to visualize the gallbladder may be a result only of impairment in the ability of the damaged liver to excrete the dye and not of gallbladder disease. Some authors have reported toxic reactions following either the ingestion or the introduction of the dye. It does not seem logical to me that one could expect a liver which cannot normally secrete bilirubin to secrete a dye. This is particularly true in cases of toxic or infective hepatitis. Many patients have been operated on for gallbladder disease because visualization of the gallbladder was not possible in the presence of jaundice, and at operation the gallbladder was found to be within the limits of normal. A flat roentgenogram of the abdomen is helpful in that it may reveal an obvious stone or tumor causing biliary obstruction.

The bilirubin that enters the intestine undergoes reduction by bacteria to form urobilinogen. A part of this is excreted in the stools and by oxidation is converted into urobilin. A certain proportion of the urobilinogen is reabsorbed into the portal circulation, passes to the liver and is almost completely reëxcreted in the bile. Any urobilinogen which may escape into the general circulation and be excreted by the kidneys becomes oxidized to urobilin after the urine is voided. Normally, however, no urobilin or mere traces appear in the urine. Quantitative estimations of urobilinogen in the urine and feces, if carried out over a prolonged period, are of value in this differential diagnosis, but obviously a single determination is of little value because of the overlapping of the values in hepatocellular and obstructive jaundice (Table 7).

TABLE 7.—EXCRETION OF UROBILINOGEN IN THE VARIOUS TYPES OF JAUNDICE

	Urobilinogen, mg. per day	
	Urine	Feces
1. Hemolytic jaundice:		
(*a*) Uncomplicated	1–10	300–1800
(*b*) Complicated by infections, anemia, infarctions, during hemolytic crises	10–300	300–2500
2. Obstructive jaundice:		
(*a*) Stone, uncomplicated	0–6	10–250
(*b*) Stone, complicated by cholangitis, anemia, etc.	4.50	10–250
(*c*) Neoplasm	0–0.3	0–5
3. Hepatocellular jaundice:		
(*a*) Cirrhosis	4–100	8–200
(*b*) Cirrhosis with increased hemolysis	20–200	300–1200
(*c*) Acute infectious hepatitis (catarrhal jaundice)	4–200	10–300

In hemolytic jaundice more bilirubin is excreted into the bile and is changed to urobilinogen in the intestine; hence more is resorbed. The urine of a patient with hemolytic jaundice therefore contains more urobilinogen and no bilirubin. In obstructive jaundice there is bilirubin in the urine, and the amount of urobilinogen depends on the amount of bilirubin that gets through to the intestine. When obstruction is complete, none gets through, and no urobilinogen is present in the urine.

In hepatocellular jaundice more bilirubin reaches the intestine in the early stages and during recovery, and less of the resorbed urobilinogen is reconverted by the liver; consequently more appears in the urine. Later, when disease is more severe, less bilirubin reaches the intestine, and less urobilinogen is present in the urine. Bilirubin itself does not appear normally in the urine. Further, in toxic or infective jaundice, urobilinogen is found in the urine.

For differentiating between obstruction caused by cancer and that caused by gallstones, the measurement of urobilinogen excretion in the feces is of value, since cancer causes complete biliary obstruction in more than 90 per cent of cases, while in only about 10 per cent of the cases of calculus and only 4 per cent of those of hepatocellular involvement is there complete obstruction, as shown by a daily fecal excretion of less than 5 mg. of urobilinogen. Absence of urobilinogen from the urine is not reliable evidence for complete obstruction.

The quantitative van den Bergh reaction, measured by the Malloy and Evelyn method, also may be of interest, but present knowledge does not offer a simple differentiation on this basis between the two types of jaundice. Massive tyrosinuria and tyrosinemia resulting from both autolysis of liver tissue and dysfunction of the aminoacid metabolism are pathognomonic of severe hepatic destruction as in acute yellow atrophy. Lesser degrees of tyrosinuria may accompany less severe hepatic degeneration and occasionally predominantly obstructive jaundice.

Early in obstructive jaundice, however, hepatic function tests give relatively normal results. The cholesterol esters make up more than 65 per cent of the total cholesterol; the intravenous galactose tolerance test and oral hippuric acid test will give normal results; the cephalin flocculation reaction will not be greater than one or two plus, and the prothrombin time, if initially low, will respond to parenteral injections of 2 mg. of vitamin K. Most of these tests give positive or strongly positive results in hepatocellular jaundice. Occasionally, however, one or two tests may give strongly positive results in obstructive jaundice, although no demonstrable hepatic destruction is present, and give negative results in hepatocellular jaundice. But if several tests are done and repeated several times, correct differentiation on the basis of the laboratory findings is relatively simple. In interpreting the results of the tests, therefore, one should analyze just what it is that they show and attempt to draw some conclusion as to the functional changes of the liver cells.

One has a choice of many different types of liver function tests in the differential diagnosis of jaundice. The cholesterol partition of the blood serum is a reliable empiric index of liver damage, although its exact physiologic significance is not yet clear. The intravenous galactose tolerance test measures the ability of the liver to convert the galactose to glycogen. Other useful indicators of the role of the liver in carbohydrate metabolism are Soskin's[31] intravenous dextrose tolerance test, which is highly sensitive and so may show abnormality even early in obstructive jaundice, and the conversion of d-lactate to glycogen. The oral hippuric acid test is less sensitive than the intravenous test, and for that reason is suited to differentiation between jaundice caused by gross hepatic damage and by simple obstruction. The cephalin flocculation test is very sensitive, depending on the nature of the plasma proteins and on other, unknown factors. Different investigators have expressed varying opinions as to its value in differentiation between obstructive and hepatocellular jaundice. Probably much depends on the sensitivity of the cephalin used in the reagents; an insensitive reagent would seem so be more suitable for differentiation than a more sensitive one. Also possibly helpful are the response of lowered prothrombin time to parenteral administration of vitamin K, the alkaline phosphatase level of the serum and examination of bile obtained through a duodenal tube.

The bilirubin in obstructive jaundice, as shown by Blankenhorn and Hoover, dialyzes through a collodion membrane, whereas the pigment hemolytic jaundice does not. This observation is in accord with the fact that the pigment of obstructive jaundice passes more readily into the tissues and urine than does that of the hemolytic type. In the former, staining of the skin and urine occurs when the serum concentration reaches 4 units (van den Bergh), whereas in the hemolytic type the concentration of bilirubin in the blood may be much higher than this without manifest jaundice. It is only when there is a superimposed inflammatory change in the liver that bile pigment appears in the urine in cases of hemolytic jaundice. Further, in hemolytic jaundice there is an increased fragility of the red cells, which is not present in other types of jaundice. Finally, careful observation of the clinical course and associated liver changes, as manifested by the various functional tests, may be the deciding factor as to the type of jaundice and particularly as to whether it is a surgical or a medical problem.

Jaundice Associated With Tropical and Allied Infections.—The increasing simplicity of world travel and the wide dispersal of the many Americans now in the armed forces throughout the world make it probable that liver disorders resulting from certain diseases will be encountered with greater frequency in the years to come. Among the most important of these diseases are yellow fever, Weil's disease, leishmaniasis (Kala-Azar), schistosomiasis and liver flukes. Also, without doubt, there will be a great increase in liver disorders resulting from malaria.

The Liver in Malaria.[21]—Hepatitis is often encountered in malaria as a result of hemolysis, anemia and toxemia. The liver is generally enlarged and hyperemic during the acute febrile attacks, and after several episodes the hyperemia may gradually be converted to a permanent passive congestion of the liver with an associated siderosis caused by deposits of hemosiderin in the hepatic cells. The malarial infection is accompanied by a decrease in liver function, according to Kopp and Solomon.[16] The saffron color of the conjunctiva resulting from excessive hemolysis is associated with an increase in the flow of bile. Possibly an excess of bile is responsible for the "bilious" vomiting and diarrhea that become especially prominent in a form of malaria called "bilious recurrent fever." The liver and spleen in this latter condition are congested and tender.

After prolonged residence in malarial regions, some persons incur blackwater fever, which is characterized by attacks of jaundice, hemoglobinuria and anemia, caused by sudden massive hemolysis. The liver parenchyma in this condition shows toxemic cloudy swelling and vacuolation with focal necrosis of liver cells and hemosiderin deposits in the cells. The Kupffer cells and endothelial cells of the sinusoids collect a black pigment during the paroxysms. Ultimately the malarial changes favor the development of portal cirrhosis, especially when other toxic factors, such as alcoholism, amebiasis and syphilis, are present.

Yellow Fever.[21]—This condition is caused by a filtrable virus transmitted by mosquitoes, usually the *Aëdes aegypti* variety, from endemic reservoirs in the Amazon basin and in West Africa.

The clinical picture is of varied intensity: It may be so mild as to go unnoticed and be recognized later by a finding that the patient's serum protects guinea pigs against infection with the virus; it may be abortive, resembling an attack of mild influenza; it may be incomplete, with a severe onset, high fever, headaches, backaches and dizziness, but without jaundice of hemorrhages or oliguria, or it may be of the classic type, in which there is a stage of active congestion for the first three or four days, with extreme prostration, backache, headache and fever. There is no jaundice in this stage, but the blood is infectious only at this time. This is followed by the stage of stasis, which lasts from one to two weeks. In it the temperature falls to normal, and jaundice appears with hemorrhages, often massive enough to cause death. Oliguria and anuria result from the liver damage, and a progressive albuminuria is more massive than one would expect to see even in the usual severe febrile disorders. There is an increasing bilirubinemia, with a lowered prothrombin time and a progressively increasing azotemia and hypoglycemia. Necropsy shows jaundice, many hemorrhages, a pale yellow, fatty liver, tense, swollen kidneys and a pale flabby heart. The liver shows a normal stroma with some infiltration of mononuclear cells and massive necrosis and fatty changes of parenchymal cells. The changes are most marked in the midzone of the lobules, and frequently the cytoplasm of the liver cells shows a hyaline degeneration with cytoplasmic hyaline bodies (the Councilman lesion). There may be also eosinophilic intranuclear masses.

The disease is self-limited, but requires active therapy for liver damage, since it usually carries a high mortality. After recovery there is usually little residual liver or kidney damage, despite the massive lesions seen when the disease has been fatal. Prophylactic immunization with a vaccine has proved effective in a number of soldiers, but there has been a definite incidence of jaundice, owing to the fact that the vaccine was made with human serum which presumably contained a contaminated virus with a predilection for the liver. The time elapsing after the injection before the onset of jaundice has been attributed by some to the slow progress of the virus along nerve tissue before it reached the liver. There have been reports of recovery of the virus from the liver at necropsy.

Leptospiral Jaundice (Weil's Disease).[11]—This condition is fairly common in Europe and Asia and seems to be increasing in incidence in the United States. It is caused by infection with *Leptospira icterohaemorrhagiae*, a spirochete carried by rats and dogs. Occasionally a similar condition may result from infection with *Leptospira canicola,* carried by dogs. The rodent population of all parts of the world contains a large proportion of infested animals and makes up the reservoir for the spread of Weil's disease.

The condition is characterized by an incubation period of four to twelve days, after which there is an acute onset of fever, prostration, muscle cramps, conjunctivitis and hemorrhagic herpes labialis. At this time there are many spirochetes present in the blood. After about the fifth day the patient enters the toxic afebrile phase, when the spirochetes disappear from the blood and appear in the urine. In this stage there are acute nephritis, hemorrhages of varied degree and jaundice in more than 50 per cent of the cases. Most of the deaths occur during this stage. After about the third week, convalescence begins. It may be interrupted by febrile relapses without the other symptoms. The spirochetes are present in the urine until about the fortieth day.

The jaundice is the most striking clinical manifestation, but while in some cases the liver may not be much affected, the kidneys are always involved. Generalized involvement of the capillaries and diffuse hemorrhages into the viscera result from the action of the spirochetes on the vessel walls. The liver is usually slightly enlarged and bile stained, and shows a centrolobular bile stasis or an active parenchymal proliferation; there may be some focal necrotic lesions. The kidneys are large and swollen, showing stromitis and tubular degeneration. The muscles show hemorrhagic lesions, and hemorrhages into the adrenal glands are frequent.

Early diagnosis can be made by dark-field examination of the centrifuged plasma, and 3 to 5 cubic centimeters of the substance should be cultured on blood agar and injected into guinea pigs if the dark-field examination gives negative results. After the first week studies should be made of the urine rather than the blood. Antibodies appear in the blood after the first week, and the agglutination, precipitation, lysis or complement-fixation phenomena can establish the diagnosis. A polyvalent antiserum is available for therapy, but it should be used before jaundice appears, since it loses most of its effectiveness thereafter. The use of parenteral liver extracts is said to be of especial value in the treatment of this condition.

CIRRHOSIS

Cirrhosis, originally designating a color of the surface of the liver, has come to connote diffuse fibrosis of the liver affecting all the lobes in about equal degree. With this fibrosis there is shrinkage, and because of the regeneration or sometimes over-regeneration of the liver cells, the liver becomes nodular or hobnailed. This irregularity of the surface is not a constant feature, as sometimes a fibrotic liver may be relatively smooth.

Mallory,[19] years ago, classified the various forms of cirrhosis. Toxic cirrhosis follows necrotizing lesions of the liver, which when severe are called acute or subacute yellow atrophy or hepatitis and when chronic are usually the result of recurrent attacks by the same etiologic factor. In this type there is a loss of liver cells which have been completely broken down. There is an absorption of the soluble material, and the insoluble material is phagocytized by the leukocytes. The stroma naturally collapses, and fibroblastic proliferation occurs. There is a sclerosis due to condensation, and the vascular framework is somewhat obliterated. This results in a small, irregular liver, the size depending on the degree of destruction and the amount of regenerated liver. The etiologic factors concerned in this type of cirrhosis were aptly classified by Bockus and Tumen[3] in their discussion of hepatocellular jaundice, which, in turn, may cause this form of cirrhosis. It is evident that alcohol may be a factor as well as the more recently reported sulfanilamide and its derivatives.

The second type, biliary cirrhosis, is a form of portal cirrhosis, and the lesions begin in the portal areas around the bile ducts. It is always associated with biliary obstruction, with or without infection. The usual causes are stones in the common duct, carcinoma of the head of the pancreas or ampulla, chronic interstitial pancreatitis, adhesions around the common duct, pressure from the adjacent peribiliary lymph glands from an inflammatory or metastatic process and ulcers of the ampulla of Vater. Moreover, biliary cirrhosis is not uncommon after surgical procedures in which the common duct is traumatized or after stricture formation resulting from choledochotomy. In the early stages the liver is large, dense and green. It may become nodular, owing to hepatic swelling and bulging of the surface lobules. Pathologically, there is evidence of inflammatory changes, with accumulation of macrophages, lymphocytes and occasional polymorphonuclear cells, which are usually accompanied by fibroblastic proliferation. An irritating effect is produced where the bile canaliculi normally join the bile ducts at the periphery. The severity of changes in the liver depends on the degree and the duration of the obstruction and the presence or absence of infection. The return of the liver to normal function depends on whether the obstruction can be relieved.

The third type, pigment cirrhosis, is a form of portal cirrhosis and is most commonly associated with an accumulation of iron-containing pigments in the disease hemochromatosis. Milder forms are seen with pernicious anemia, particularly after a large number of blood transfusions. A few cases have been reported in workers with copper. The irritating pigments and the metals collect around the periphery of lobules and cause a macrophage and fibroblast proliferation from the periportal connective tissue. The size of the liver is unaffected, and the surface is usually smooth.

The fourth type, fatty cirrhosis, in which the lesions develop around the lobules, joining the portal areas in continuous bands of fibrous tissue resulting from the pressure of atrophied cells and hyaline and fatty degeneration of the cells at the periphery of lobules, is followed by fibroblastic proliferation and is most commonly seen in chronic alcoholic addicts and patients affected with diabetes mellitus. It can be experimentally produced with carbon tetrachloride and phosphorus poisoning and is often found in depancreatized dogs. It may occur with hypothyroidism or with lesions of the pituitary and midbrain, as in cases of progressive lenticular degeneration (Wilson's disease). The fatty infiltration is usually due to defects in the sugar and fat metabolism. The storage of fat in the liver markedly reduces the respiratory quotient. Himwich and Fazekas[13] have recently shown that the respiratory quotient of the liver tissue itself in experimental diabetes goes as low as 0.57, far below that found when fat alone is being consumed. With such a low carbon-oxygen ratio, little carbohydrate is utilized. Peters and Van Slyke[25] have shown that alcohol interferes with carbohydrate metabolism and fat oxidation because of its action as a cell and tissue toxin. These factors, when associated with starvation or a high fat and low carbohydrate diet, allow the liver to accumulate a large amount of unoxidizable fat. The liver cells, therefore, will be deprived of oxygen and nutrition. If the process is continued and an anoxia of the cells becomes pronounced, slow atrophy results, which may, in turn, produce hyaline degeneration of the cytoplasm.

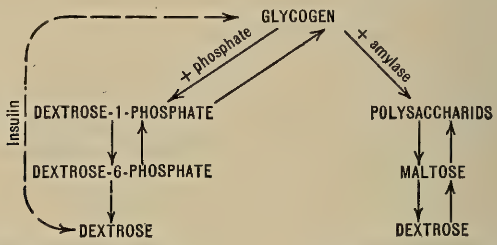
The conclusions of Conner[5] show that alcoholic cirrhosis produces changes in the liver because of the following: (1) starvation, or partial starvation, and the continuous use of large amounts of alcohol, which produce fatty liver from which the patient may die before cirrhosis develops; (2) a diet restricted to protein and fat, plus alcohol; (3) a diet containing some, but an insufficient amount of, carbohydrates and vitamins, plus large amounts of alcohol taken habitually (this diet may prolong the time of development of cirrhosis by years); (4) periods of sufficient diet plus alcohol, alternating with periods of severe alcoholism with an insufficient diet, these periods coming so close together that in the interim the liver has not had time to return to normal.

Experimentally, a fatty liver can be produced by carbon tetrachloride or phorphorus administration, by depancreatization (possibly because of a deficiency of the fat hormone, lipocaic), by a high fat or a high cholesterol diet or by various nutritional deficiencies. (Deficiencies of the various factors of the vitamin B complex, a deficiency of dietary choline and methionine or a protein deficiency of enough magnitude to cause hypoproteinemia have all been shown to cause fatty liver.) An excess of biotin can cause fatty liver, as does an excess of the aminoacid cystine. These experimental findings suggest that portal cirrhosis in man, at least in some cases, may result from similar nutritional deficiencies or imbalances, especially since Chaikoff and associates[4] have shown definitely that prolonged fatty infiltration of the liver leads to cirrhosis. In view of the fact, however, that some substances have been found to protect against the development of fatty liver or cirrhosis under certain conditions and to facilitate the production of these lesions under other conditions, the clinical significance of these nutritional experiments is not yet definitely established.

The importance of syphilis and the treatment of this disease has been repeatedly emphasized in the causation of cirrhosis. Some syphilographers, however, are doubtful that the continuous treatment of syphilis over long periods is an important factor in the development of chronic hepatic disease. However, Baldridge[2] emphasized that antisyphilitic treatment is a factor, and his report on a series of 36 patients with cirrhosis showed that one-third had a history of treatment for syphilis. Approximately 25 per cent of the patients undergoing intensive antisyphilitic treatment showed some change to the liver. Kellogg, Epstein and Kerr[15] reported an incidence of 19 per cent abnormal hepatic function as shown by an excretion test (rose bengal) in a group of 90 patients with untreated syphilis. Further, in 5 of 29 patients originally having normal function, antisyphilitic therapy caused transitory disturbances in hepatic function. In addition, 4 of 18 patients with initially abnormal function had further impairment and an increased tendency to untoward reactions following antisyphilitic therapy.

In portal cirrhosis, which has been previously described as atrophic cirrhosis of Laënnec, the symptoms are dependent on the degree of change in the liver. However, it is to be borne in mind that this disease, insidious though it be, may be entirely symptomless until it has reached its decompensated state. In patients who have a passive hyperemia of the gastrointestinal tract, particularly of the gastric and intestinal mucosa, nausea, loss of appetite, rapid loss of weight, morning vomiting, irregular bowel movements, sallow skin, "muddy" complexion, coated tongue and a foul breath may be prominent, and if the condition goes on long enough, esophageal varices may develop and may lead to hemorrhage with often fatal results. Hemorrhoids are common and may be the initial symptom that gives rise to the suspicion that a patient has portal cirrhosis. Profuse hemorrhage into the bowel, causing melena, is not an uncommon symptom, and gives rise to severe secondary anemia. Macrocytic anemia is a frequent finding in all instances of advanced or chronic hepatic injury. The anemia is supposed to be dependent on the failure of the liver to store the active hemopoietic principle or on its inability to present the principle to the body in a proper form for utilization.

The disturbance in carbohydrate metabolism, manifested by hyperglycemia or hypoglycemia, is the outstanding and most constant result of severe injury to the liver. The liver has at least three separate functions directly concerned with the metabolism of dextrose: (1) glycogenesis; (2) glycogenolysis, and (3) the production of dextrose and the deposition of glycogen from noncarbohydrate precursors (glycogenic aminoacids and glycerol fractions of fats). The balance between glycogenesis and glycogenolysis allows the liver to function as a storehouse of readily available dextrose to be delivered into the blood stream in times of need. If, for instance, the glycogenesis alone were impaired, the hypoglycemia noted during fasting could be due to insufficient storage of glycogen in the liver, even though the glycogenolytic function was normal. On the other hand, the impaired conversion of glycogen to dextrose could account for the hypoglycemia without involving the glycogenic mechanism. This would result in the retention of an abnormally large amount of glycogen in the liver. Gierke's disease illustrates a type of hepatogenic hypoglycemia, the mechanism of which appears to be wholly on the basis of the disturbed glycogenolysis. In this disease the liver has a great excess of glycogen, indicating no disability in its deposition. Therefore, chronic hypoglycemia may be due to a deficient glycogenolytic mechanism. In the presence of toxemia and especially after gallbladder disease of long duration, the glycogenolytic function of the liver may be increased pathologically by increased amylase activity.[32] This increased glycogenolysis results in hyperglycemia, and frequently the patient is treated for diabetes mellitus. Insulin, however, further depletes the storage of glycogen by the liver, thereby lowering the resistance of the liver to toxins still more. I have suggested[26] that this condition be called the "cholecystohepathohyperglycemic and glycosuric syndrome" until a better name is found. It is distinguished from diabetes mellitus by the dextrose tolerance curve, which is that of liver disease rather than that of diabetes. Intravenous dextrose therapy halts the amylase breakdown of glycogen by the effect of the law of mass action on the chemical system, glycogen$\rightleftarrows$dextrose, improving the liver storage of glycogen (Fig. 92). Other liver functions also improve. Accurate evaluation of this syndrome, followed by cholecystectomy, substitutes a life of well-being for one of invalidism.



Glycogen breakdown in normal liver (phosphorylation by means of enzymes). Insulin most probably acts in this system.

Amylase breakdown of glycogen in "toxic" liver. Insulin does not act in this system. Dextrose, however, can inhibit the breakdown by mass action.

FIG. 92.—Diagram of the breakdown in the liver of glycogen to sugar (glycogenolysis,) which is faster than its storage (glycogenesis).

Further, it has been shown that with liver damage caused by arsphenamine poisoning in dogs there are associated a fall in the concentration of chlorides of the plasma, the development of acidosis and an increase in the content of lactic acid in the blood, along with a consistent hemoconcentration. The metabolism of chlorides with this condition is not clearly understood. The later elevation of the concentration of urea and of nonprotein nitrogen may depend on renal failure associated with hepatic insufficiency.

With certain poisonings, anoxemia, resulting from hepatic injury, may be a factor. According to Snell and Keys,[30] it appears to depend on a decrease in the affinity of hemoglobin for oxygen, shown by displacement of the oxygen dissociation curve to the right. They stated that whether this should be attributed to some fundamental peculiarity of hemoglobin or to the admixture of other substances in the blood interfering with normal respiration is as yet undetermined.

One of the most serious manifestations of parenchymatous injury of the liver is hepatic insufficiency. Like the uremic state, it is not very well understood. It does not closely simulate the syndrome produced by hepatectomy in animals. However, there are disturbances of carbohydrate metabolism that may be severe. With this condition the patient generally becomes exceedingly anxious about himself and is apprehensive; the pulse becomes very rapid; he may break out in a cold perspiration; slight cyanosis may be evident about the face, and later convulsive seizures may be not uncommon. The temperature as a rule becomes subnormal, and when the process is severe enough, in spite of the therapeutic approach, the patient usually dies.

This clinical syndrome often suggests acute intoxication and probably represents the failure of normal processes of detoxication of the liver. Since the liver is the first line of defense against endogenous and exogenous toxins, when it fails in this function the load may fall on the kidneys, with resulting renal insufficiency. In experimental animals, a consistent hemoconcentration also has been shown. In human beings, there is some concentration of the blood, though it never reaches so severe a degree, and hypochloremia may occur. Elevation of the concentration of urea and of nonprotein nitrogen in the blood may be associated with a coëxistent renal failure. Acidosis, manifested by low carbon dioxide–combining power and the changes in the pH of serum, has been observed. As previously stated, the anoxemia, manifesting itself in the clinical cyanosis, may be dependent on a decrease in the affinity of hemoglobin for oxygen in liver disease. Finally, chronic atrophy or cirrhosis may develop on the basis of repeated episodes of acute injury to the liver, and when these changes take place, the associated findings of either hypertrophic biliary or atrophic cirrhoses may become evident. The clinical picture of this condition need not be repeated at this time.

Hemorrhage associated with disease of the liver may result from the rupture of the collateral circulatory channels or may be dependent on some intrinsic change in the coagulating properties of the blood. Hemorrhages resulting from the former condition are well known in clinical medicine, but it is only recently that Quick and his associates[27] have clarified the question of the intrinsic change in the blood *per se*. They were the first to note that the deficiency was probably that of the prothrombin of the blood, all other elements necessary for the coagulation being present in normal amounts. This has been corroborated by other investigators.

Hawkins and Brinkhous[12] have noted, in studying the hemorrhagic states induced by complete biliary fistula in dogs, that a deficiency of prothrombin was present and could be corrected by the feeding of bile. This would seem to indicate that one of the factors needed to maintain the normal level of prothrombin is the presence of bile in the bowel. Bile is necessary for the proper assimilation of an additional factor, vitamin K (coagulation vitamin), which has been shown experimentally in the unsaponifiable nonsterol fraction of hog liver and in alfalfa. Thus these two factors, the presence of bile in the bowel and the hypothetical fat-soluble vitamin, are important in maintaining the normal level of prothrombin. In addition, changes in the liver itself may produce a difference in the prothrombin concentration and its manufacture. The latter factor may be associated with toxic changes in the liver. It was formerly thought that the coagulation of blood in the presence of liver disease was associated with a disturbance of calcium metabolism, but more recent clinical and experimental evidence has shown this not to be a fact.

As the disease progresses, ascites develops; fluid becomes percussible in the flanks, and the abdominal phase becomes more prominent. Marked ascites may cause difficulty in respiration. At this stage the spleen is usually palpable, enlarged, hard and firm. As a rule the urinary output is decreased, and bilirubinemia may exist. It may not be clinically evident but may become more pronounced because of the superimposed toxic hepatitis. Mental symptoms, such as depression, headache, loss of memory, drowsiness, delirium, confusion and even coma, are not uncommon.

Changes in serum albumin and globulin in hepatic disease have been recognized for many years. Grenet[11] and Gilbert and Chiray[9] were among the first to note the decrease in concentration of total protein in patients with cirrhosis of the liver; their observations were later confirmed by Filinski[7] and Abrami and Wallach.[1] More recently Myers and Keefer,[22] in a study of 16 patients with cirrhosis of the liver, found that the total plasma protein value, particularly the albumin fraction, is always decreased. This was confirmed by Tumen and Bockus[33] and by Foley and others.[8] Snell[29] found that an alteration in the albumin-globulin ratio may be of some prognostic significance. Gray and Barron[19] have demonstrated the marked increase in gamma globulin and decrease in serum albumin caused by liver disease and especially by cirrhosis. This has already been referred to in the discussion of liver function.

Other functional tests of liver disease show definite impairment of liver function in cases of cirrhosis, the degree depending on the etiologic factor and the extent of pathologic changes.

Diagnosis.—The diagnosis of early disease depends on a history of some etiologic factor, particularly use of alcohol or other hepatocellular poisons. The deviations from normal expressed by the various liver functional tests are exceedingly helpful. Frequently one is able to obtain a biopsy specimen, which can be done in the course of a laparotomy instituted for some other cause. Further, a history of malaise, loss of weight, dyspepsia or one or more episodes of slight jaundice may suggest liver involvement. A palpable, firm liver should direct attention to the possibility of cirrhosis. The vomiting of blood, the passing of black stools and the presence of hemorrhoids in unconstipated persons may be significant evidence. Later, when the picture, particularly of portal cirrhosis, becomes more or less "full-blown," the presence of ascites and dilated superficial abdominal veins makes the diagnosis relatively simple. Frequently diagnostic paracentesis and the finding of a clear fluid of low specific gravity with comparatively few cells are of definite corroborative value. One must bear in mind, however, that frequently a tuberculous peritonitis is engrafted on simple transudation into the peritoneal cavity and may confuse the clinical picture.

Certain special types of cirrhosis merit further consideration:

Hanot's Hypertrophic Biliary Cirrhosis.—The hypertrophic nonobstructive biliary cirrhosis of Hanot is less common than obstructive biliary cirrhosis. It is probably caused by persistent inflammation of the smaller intrahepatic bile ducts; the liver is enlarged, and the cirrhosis intralobular, since the fibrous tissue invades the lobules. In the later stages necrotic changes of the hepatic epithelium also appear. The liver is stained with bile, as are the nearby viscera frequently. The spleen is large and fibrous.

Clinically, the disease is featured by a general persistent malaise. Abdominal distention with hepatomegaly and splenomegaly appear, and at about the same time jaundice may become prominent. The jaundice varies in intensity and duration, recurs frequently and finally becomes persistent. Abdominal pains, fever and pruritus occur at intervals. The course is progressively downhill, and the disease is usually fatal within three years. Hanot's cirrhosis is to be differentiated from Laënnec's cirrhosis by the fact that it occurs more often in younger patients, by the absence of a history of alcoholism, by the intense greenish hue to the jaundice, by the absence of ascites and by evidence of marked portal obstruction till the final stages of the disease, despite marked hepatomegaly and splenomegaly.

Hemochromatosis.—Hemochromatosis is a type of pigment cirrhosis. It seems to vary in incidence in different parts of the United States, and the highest incidence was found by Mallory[19] at the Boston City Hospital, an institution at which alcoholic and cirrhotic patients constitute a relatively large proportion of admissions. Only 15 cases of definitely established hemochromatosis in the female have been recorded in the literature. In this disorder hemosiderin, an iron-containing pigment, accumulates in many tissues of the body, especially the liver and pancreas. A nonferrous pigment, hemofuscin, also is present in large amounts. Cirrhosis of the liver with enlargement of the liver and large amounts of hemosiderin deposited in the cells is characteristic of the condition. The amount of copper in the liver also is increased. Associated degeneration of glandular cells is found, and when the islets of Langerhans are affected, diabetes mellitus results. The diabetes tends to increase progressively in severity and is characterized in some cases by marked insulin resistance, possibly because of the derangement in the liver's rate of output of dextrose, and in others by marked variability in insulin sensitivity, because of a depletion of hepatic glycogen.

Frequent symptoms are asthenia, which seems to depend on the nutritional disturbance, and a bronzed pigmentation, resulting from deposition of hemosiderin in the skin as well as an increase in melanin. Physical signs are the increased pigmentation of the skin, hepatomegaly and splenomegaly, cardiac enlargement and failure, testicular atrophy from pigment damage of the cells and portal hypertension. The diagnosis is made by demonstration at biopsy of increased iron in the skin or of hemosiderinuria as a consequence of an accumulation of hemosiderin in the kidneys. The course varies from patient to patient.

The cause is unknown. There is a disturbance in iron metabolism, but whether this is primary or secondary is not known. Mallory suggested that the disorder is the result of chronic poisoning by excessive amounts of copper.

Treatment resolves itself into specific treatment of the liver disease and of any associated diabetes.

Wilson's Disease.—This condition, also known as hepatolenticular degeneration, is characterized by degenerative changes of the basal ganglions of the brain, associated with portal cirrhosis. It is familial and hereditary; the cause is unknown. Usually manifestations of hepatic disease, such as vomiting, transient jaundice, ascites, hepatomegaly, splenomegaly and decreased liver function, become evident before the neurologic changes, which consist of contractures, extrapyramidal rigidity, dystonic movements, tremor and mental deterioration. A brownish green pigment ring around the cornea, the Kayser-Fleischer ring, is pathognomonic of the disease. No specific therapy is available, and the course is usually downhill, terminating within several months to several years in death from an intercurrent infection or disease.

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GENERAL TREATMENT OF LIVER DISEASE

Certain general measures are applicable in the treatment of all types of liver disease. The recognition of the cause of the liver disease is necessary to effective therapy, and removal of the etiologic factors assumes a major role whenever they can be determined. In the treatment of jaundice one is constantly confronted by the immediate question whether one is dealing with a medical or a surgical problem.

It is preferable that the treatment be carried out in a hospital, where repeated studies of the progress of the disease may be made. When the liver damage is more than minor, it is probably best also to keep the patient in bed. The use of drugs should be avoided as much as possible, and it should be kept in mind that even the commonly used barbiturates and sulfonamides can probably impair the function of the normal liver and constitute an added strain on a damaged liver. Constipation also is an added strain, and should be treated with mild laxatives. The cholagog salts are useful as laxatives. I personally prefer effervescent sodium phosphate or magnesium citrate rather than the harsher forms, such as magnesium sulfate, which I feel irritate the intestinal tract too much.

Patients with liver disease in general have a lowered resistance to infection. Careful attention to general hygiene and especially to the avoidance of contacts with persons suffering from colds or other respiratory infections is, therefore, of major importance.

Dietary regulation is an essential part of the treatment of liver disease. An early return of normal eating habits is one of the most important factors in the improvement of liver function after the liver has been damaged. The food should be palatable and served in an appetizing fashion, and feedings should be given at frequent intervals. Nothing is so depressing to the patient as to have an ill-kept tray brought in. He has little desire for food, and one should use every psychologic effort to encourage an added caloric intake. Ravdin and his associates[16] stated that a caloric intake in excess of basal requirements is most important in protecting the liver and aiding repair of liver damage.

A high fat diet increases the fat content of the liver, and thereby its vulnerability to toxins, and possibly itself damages the liver. The diet, therefore, should be low in fat. A small amount of fat, however, is necessary for palatability, for furnishing vitamins and possibly for furnishing essential fatty acids.

It is generally accepted that destructive or degenerative hepatic lesions are best treated with large amounts of carbohydrate. Such treatment increases the glycogen content of the liver and in doing so also puts the liver at rest, decreases ketosis, inhibits fatty infiltration, aids in detoxication, spares the proteins of the liver cells and probably protects the colloid structure of those proteins. High carbohydrate diets have been shown to be protective in liver damage caused by obstruction to the common bile duct, partial hepatectomy, Eck fistula and various hepatotoxins. Clinical studies have demonstrated the same protective value in liver disease.

A difference of opinion exists, however, concerning the advantages of intravenous dextrose therapy if the patient can take the "necessary" dextrose or carbohydrate by mouth.[3] Now, the "necessary" amount of carbohydrate is that amount sufficient to raise the blood sugar to a level which will suppress hepatic sugar output. But while the normal liver will respond to the usual postprandial hyperglycemia, the "irritable" liver of acute toxemia may require a much higher blood sugar concentration to inhibit hepatic sugar formation. That this is so is seen in the prompt curtailment by the acutely poisoned liver of its output of sugar when large doses of dextrose are given intravenously, while small doses have little or no effect.[23] Furthermore, as Cori and Cori[6] have pointed out, for the normal liver "the blood sugur concentration and not the amount of glucose administered must be regarded as important for the rate of glycogen deposition in the liver." Consequently, when an attempt is made to protect a damaged liver by means of glycogen deposition therein, the blood sugar concentration may have to be raised to a level impossible to reach by ingestion of carbohydrates. In such cases, the intravenous infusion of dextrose is essential. The fact that extreme hyperglycemia so produced may result in glycosuria should not deter one from such vigorous therapy. Wakim and Mann[24] have shown that regeneration of hepatic tissue after injury begins in islands of normal cells that are supplied mainly by arterial blood, while the cells in areas supplied only by portal vein blood may be too badly injured to regenerate. If the cells from which regeneration is to originate are to receive the full benefit of high dextrose concentration so that they can begin to restore liver parenchyma, the hyperglycemia following intravenous therapy is desirable.

Because of the glycosuria which may result from intravenous dextrose therapy, some physicians favor the routine use of insulin with the sugar. However, unless the patient has diabetes, the indiscriminate use of insulin may defeat the purpose of dextrose administration. Soskin, Allweiss and Cohn[21] have shown that in the presence of sufficient insulin to maintain a normal constant blood sugar level, no additional insulin is necessary to obtain a normal hepatic response to administered sugar. The injection of insulin into the nondiabetic person can therefore produce no additional hepatic effect, but does cause increased storage of glycogen in the muscles. This peripheral effect causes a fall in blood sugar, which in turn stimulates the liver to pour out more sugar. Thus, the liver is deprived of glycogen rather than the reverse. Mantaining the hyperglycemia in spite of the administered insulin will prevent this reversal in effect, but will not be more beneficial than the giving of the same amount of sugar without insulin. Soskin, Allweiss and Mirsky[22] have shown that the use of insulin with dextrose, as compared with the use of dextrose alone, in the treatment of toxic, nondiabetic animals shortens life. After prolonged treatment by intravenous dextrose injections designed to suppress the sugar-producing mechanism of the liver, that organ requires time to recover from the inhibition of dextrose formation, so that hypoglycemia may appear one to three hours after cessation of the infusion.[20] This should be anticipated, and treated with small doses of carbohydrate by mouth or intravenously if necessary. Many patients with atrophic cirrhosis and associated ascites have been definitely relieved by the daily parenteral injection of hypertonic dextrose solution, which not only is a factor in liver repair but acts as a diuretic agent. However, for prolonged, overwhelming changes of the liver, this treatment may not produce as striking results as for early disease.

Proteins are of value in the diet in allowing hepatic regeneration to proceed at a maximum rate, since the proteins are necessary for cellular repair. Proteins also protect against toxins, but in general less effectively than do the carbohydrates. The proteins must be preponderantly of vegetable or dairy origin, since meat extracts for some reason are injurious in liver disease.

It has been demonstrated in both laboratory and clinical studies that vitamin administration protects against liver damage and aids in recovery from hepatic lesions. The viatmin B complex has been found to be especially active in preventing fatty liver and so be of value in the treatment of cirrhosis and hepatic failure. Since it also furnishes valuable proteins, brewer's yeast, in doses of 30 to 50 Gm. per day or in the form of liquid concentrates, is one of the most effective forms of vitamin B for treatment of liver disease. Vitamin C administration is of value in protecting against some hepatotoxins and is used therapeutically to protect some of the enzyme systems and improve resistance of the liver cells. Vitamin A deficiency is common in liver disease because of impaired absorption resulting from bile deficiency, from impaired conversion of carotene to vitamin A and from fixation of vitamin A by areas of damaged liver parenchyma. Vitamin D absorption is also defective because of biliary deficiency. To prevent these deficiencies and for their possible protection against loss of glycogen from the liver, supplementary doses of these vitamins should be added to the diet.

Associated with the decreased flow of bile into the intestine in jaundice is a deficient absorption of vitamin K, and when the liver is damaged there is also a decreased production of prothrombin independent of the absorption of vitamin K. Hypoprothrombinemia results from inadequate absorption or use of vitamin K and is responsible for much of the hemorrhagic tendency that is common in liver disease. Capillary damage and formation of abnormal blood clots are also important factors in this hemorrhagic tendency, however, and it should be recognized that hemorrhage is not always associated with hypoprothrombinemia. Aggeler and Lucia,[1] nevertheless, suggested that it is advisable to administer vitamin K to all patients with liver disease or jaundice regardless of the prothrombin time or bleeding time. It is most important to prepare such patients well for operations; a dose of 1 to 4 mg. of vitamin K parenterally on at least four days before operation and four days after operation is suggested as a good routine practice. Usually a dose of 1 to 5 mg. of vitamin K parenterally, or 3.6 to 10 mg. orally with 0.3 to 0.6 Gm. of animal bile salts, will bring the prothrombin time to a maximum in twenty-four hours, and the effect will persist for four days. Where liver damage is so severe that there is little response to vitamin K therapy, an infusion of 500 cubic centimeters of undiluted plasma will usually correct the hypoprothrombinemia to well beyond the danger point (60 per cent of normal).

Recent evidence by Meyer and Howard[14] showed that the oral administration of acetylsalicylate and sodium salicylate to human beings in daily doses of 20 to 80 grains consistently produced hypoprothrombinemia and hypocoagulability of the blood. This may be prevented by administration of vitamin K with the salicylate. Hemorrhagic manifestations with acute rheumatic fever may, in some cases, be due to large doses of salicylates.

Similarly, Shapiro and associates[18] reported that in man, as in the rat, salicylate in adequate doses induces prothrombinopenia, which can be prevented by administration of vitamin K if liver function is adequate. Cirrhosis of the liver and preëxisting prothrombinopenia augment the effect of salicylate. Acetylsalicylate appears to be more potent than sodium salicylate. The salicylates act, apparently, in the same way as dicumarol, but less effectively. They can complement dicumarol to avoid excess prothrombinopenia.

On the basis of this evidence, one might sound a note of warning as to the indiscriminate use of salicylates in diseases of the liver, and particularly those associated with jaundice.

Several of the substances that have been shown to possess lipotropic activity have been used therapeutically, especially for patients with fatty liver or active cirrhosis. Choline chloride in daily doses of 1 Gm. is said to be of value here.[4] Diets that yield large amounts of lecithin and methionine also are said to be useful. The administration of lipocaic, raw pancreas or pancreatin also might be effective in special cases. Crude aqueous liver extract, in addition to its lipotropic activity, seems to aid in detoxication and is definitely a part of the therapeutic regimen of severe liver disease. Its activity depends partially on its content of xanthine and partially on other, unknown factors.

An important symptom in liver disease which requires special attention is anemia, due in part to failure of absorption of iron because of the formation of iron soaps. Administration of iron salts, therefore, may not be successful in correcting a hypochromic anemia caused by liver disease until the normal bile flow is restored. The macrocytic anemia seen with the more severe liver damage is treated parenterally with liver extract, but does not respond as well to this therapy as does pernicious anemia, until the process causing the liver damage becomes quiescent.

Calcium deficiency is another defect in mineral metabolism associated with liver disease. This deficiency is caused by the lack of bile, resulting in impaired absorption of calcium and of vitamin D, and possibly by an excessive requirement for calcium when hepatotoxins are present. Calcium diminishes the hepatotoxic action of carbon tetrachloride and of certain other toxins. However, the experimental evidence for calcium therapy is controversial; that it can do no harm is evident, and one may therefore use it because occasionally a patient may be benefited.

For some time I have advocated the use of potassium iodide in cases of jaundice, because it seemed to me that the bilirubinemia disappears more rapidly after the use of this salt in doses of 10 to 20 grains three times a day. If there is a syphilitic factor, the indication for the use of iodides is definite. Arsenical should never be used in the treatment of syphilitic conditions when there is evidence of liver damage. Mercury or bismuth salts are the preferable drugs.

Hemorrhage in liver disease, as has been mentioned before, may be due to the rupture of collateral circulatory channels. The bleeding from esophageal varices may require surgical intervention. While sphenectomy may be advantageous for certain diseases, such as "Banti's disease," the removal of the spleen in patients with portal cirrhosis does not seem justifiable, because of the risk involved. Other technical means of controlling hemorrhage from collateral circulation have been suggested, but these should be used only as a last resort.

Bile salts are used by many clinicians in treating liver disease when there is an obvious need for such therapy to improve the digestion and absorption of fatty acids, vitamins, iron and calcium. Bile salts also exert a desirable laxative action and possibly are bacteriostatic and bring about some detoxication in the intestine. In acute hepatitis, bile salts exert little choleretic effect, although they are frequently used for that purpose. Little harm has been found to result from such therapy, but it is in effect "whipping up a tired horse." Greene and Farrell[12] described a case of possible acute yellow atrophy following treatment with intravenous bile salts and cautioned against such therapy without definite indications. Hydrocholeretics are the oxidized unconjugated cholic acid derivatives, such as dehydrocholic acid, decholin and ketochol; these produce an increased volume of less viscid bile poor in total solids. Choleretics are the conjugated cholic and ketocholanic acids, such as Fel Bovis; they produce an increased volume of bile rich in bile salts. The hydrocholeretic sodium dehydrocholate is used parenterally to flush the biliary passages and increase drainage. It is usually stated that bile salts are contraindicated when there is acute liver damage and in complete obstruction since the bile salts are retained. Ivy,[13] however, noted no harmful results in animal experiments.

Natural bile salts are used in doses of 5 to 15 grains daily, and the oxidized salts are given in doses of $3\frac{3}{4}$ grains several times daily. The use of these agents, except for replacement therapy in biliary obstruction or bile fistula and to aid absorption of vitamin K, is still of questionable value.

Fatty metamorphosis of the liver, associated with diabetes mellitus, has been treated with lipocaic. Evidence supporting this treatment is to be found in the observations of Fisher[9] and Allan, Bowie, Macleod and Robinson,[2] that depancreatized dogs treated with sufficient insulin to control the diabetic symptoms show signs of hepatic insufficiency, become insulin sensitive and die in a state of hypoglycemia within one to eight months. Necropsy studies revealed a marked fatty infiltration and degeneration of the liver as the principal or sole abnormality. By the addition of raw pancreas to the diet, Allan and his co-workers were able to prevent such hepatic changes and to permit survival for a long time. Dragstedt, Prohaska and Harms[7] prepared a fat-free alcoholic extract of beef pancreas (lipocaic) which, when fed to depancreatized dogs, proved as effective as either raw pancreas, lecithin or choline. They expressed the belief that it is a "fat-metabolizing hormone" concerned in the normal transport and utilization of fat. Dragstedt and his co-workers[8] administered lipocaic to patients manifesting diabetes mellitus in association with hepatomegaly and noted a decrease in the size of the liver. Similar observations were made by Grayzel and Radwin[11] in 3 cases of juvenile diabetes mellitus treated with a pancreatic extract prepared according to the method of Dragstedt and his associates. Snell and Comfort[19] also reported a rapid decrease in the size of the liver and an improvement in the hepatic function during the first twelve days of lipocaic therapy. More recently, Rosenberg[17] reported proved recovery after treatment with lipocaic of a patient with fatty metamorphosis of the liver associated with diabetes mellitus. Biopsy studies were made before and after treatment and were correlated with the results of liver function and dextrose tolerance tests, cholesterol determinations and clinical course. The changes observed represented the clinical counterpart of the findings noted in experimental animals.

The transduodenal drainage of Lyons and Meltzer has been advocated by some for the medical treatment of jaundice. I personally do not feel that this method of treating jaundice has any advantage over the time-honored methods of causing excretion of bile. Furthermore, I can see the dangers of taking large amounts of bile out of the intestinal tract, because in jaundice there is a smaller amount of bile than normal present, and the taking out of this bile by transduodenal drainage may remove some of the factors necessary for normal digestion and particularly for the absorption of certain vitamins. With physicians who use transduodenal drainage for diagnostic purposes I have no quarrel, but as a therapeutic measure in the treatment of jaundice I can see no especial claim for its benefits.

The treatment of ascites and edema, which may complicate the picture of cirrhosis, is dependent on the improvement of the condition of the liver, the decrease of the portal venous pressure and the elevation of the concentration of proteins of the plasma, which increases the colloidal osmotic pressure of the serum. The Talma-Morrison omentopexy has been somewhat disappointing for the reduction of the portal venous pressure. Fuller and her collaborators[10] have suggested a partial enterectomy for reducing the portal venous flow. This has never appealed to me as a logical approach to the problem. The elevation of the concentration of proteins in the plasma seems to offer a greater prospect of success than omentopexy or partial enterectomy. Centurion[5] attempted to accomplish this by reinjecting the ascitic fluid and, by virtue of the content of albumin of this material, occasionally achieved the desired result. Routte's operation[15] of permanently draining the ascitic fluid into the proximal end of the saphenous vein (venoperitoneostomy) has been employed with good results. However, other methods should be tried before this is resorted to.

The Therapeutic Regimen.—The patient should be hospitalized and preferably at bed rest. His diet should consist of frequent feedings and should have a caloric value of 3,000 or more. It should contain from 350 to 500 Gm. of carbohydrate, 100 to 150 Gm. of protein (avoiding meat and fish as much as possible) and about 20 Gm. of fat, or slightly more if necessary for palatability. Condiments and spices are best avoided, and all alcoholic liquors are to be proscribed.

Proper fluid and mineral balances should receive careful attention, and watch should be kept for evidences of hypohydration or of water retention. When ascites appears to be imminent, restriction of fluids to 1,200 cubic centimeters daily or less and use of a salt-poor diet or acid-producing salts may be necessary. Mercurial diuretics may cause fatal hepatic and renal insufficiency and probably should be avoided entirely in the treatment of ascites caused by liver disease.

Paracentesis entails less risk and may be resorted to frequently without greatly interfering with the general condition of the patient. Care must be taken not to withdraw too much fluid at one time or to withdraw it too quickly. Further, peritoneal shock should be prevented by carefully anesthetizing the peritoneum. Hypodermic solutions of atropine and epinephrine should be close at hand in case the patient suffers from the effects of peritoneal shock.

Brewer's yeast in divided doses, amounting to 30 to 50 Gm. per day, or liquid concentrates of yeast are to be used when tolerated, especially in cases of cirrhosis. Citrus fruit juices, 250 to 360 cubic centimeters daily, should be used as a source of vitamin C. Vitamins A and D in doses of 25,000 to 50,000 international units one or two times daily are of definite value. The vitamin B furnished by the brewer's yeast may be supplemented with parenternal thiamin in 10 to 20 mg. doses and parenteral niacinamide in 50 to 100 mg. doses, especially in cases of severe liver damage, when liver extract in doses of 30 cubic centimeters orally three times daily or 3 to 5 cubic centimeters of crude parenteral extract two or three times per week also should be used. Choline chloride, 1 Gm. per day, may be of value also, as may 10 per cent calcium gluconate in doses of 10 cubic centimeters intravenously daily.

Intravenous administration of dextrose in one of the most powerful therapeutic measures in the physician's armamentarium for the treatment of liver disease. As has been previously stated and reëmphasized here, it is all important to maintain the glycogen content of the liver cell. For this, several measures are suggested. If ascites is present, one should start with concentrations of 50 per cent dextrose in volumes of 100 to 200 cubic centimeters daily, continuing until the output of fluids exceeds the intake. After this, 300 to 400 cubic centimeters of aqueous 25 per cent dextrose solution should be kept up until there is another demonstrable increase in the output of fluid, when one may resort to 10 per cent aqueous dextrose solutions in volumes of 3,000 to 4,000 cubic centimeters daily. If at any time during this regimen the output of fluids is less than the intake, one may have to resort as before to the more concentrated solutions to restore the fluid balance. It is important that the blood chloride level should be frequently determined; should this show any diminution, chloride solutions of dextrose should be substituted in sufficient concentration to maintain a normal chloride balance. It is also to be reëmphasized that thiamin chloride in doses of 20 to 30 mg. should be given intravenously at the same time for each 100 Gm. of dextrose injected, to insure the complete utilization and metabolism of the dextrose.

If the patient is unable to eat a full diet, it may be well to administer infusions of aminoacids in doses adequate to maintain the normal nitrogen balance. Reactions to the aminoacid preparations, however, may increase the damage to the liver; hence such infusions should be carried out slowly and carefully.

When there is marked hypoproteinemia or anemia, frequent small blood transfusions or infusions of plasma may be used with benefit, although such treatment may not be effective in raising plasma proteins until the liver disease has reached a quiescent phase.

For treating the hemorrhage tendency, plasma or blood transfusion is of value, especially when 1 to 5 mg. of vitamin K administered parenterally for several days has not raised the prothrombin time to a safe level.

When in spite of these measures, ascites develops and causes discomfort to the patient, paracentesis should be done, and mild diuretics should be given. Patients suffering from surgical jaundice should receive intensive preoperative treatment to protect the liver during and after operation. Especial attention should be paid to the preoperative administration of vitamin K and the intravenous infusions of dextrose. Here again, 3,000 to 4,000 cubic centimeters of aqueous 10 per cent dextrose solutions should be used daily.

It may not be amiss at this time to reëmphasize the importance of cholecstectomy and common duct exploration where indicated as a therapeutic measure in the treatment of liver disease. It is well established that cholecystitis usually produces hepatitis, the degree depending on the resistance of the liver on one hand and the severity of the inflammatory process in the biliary tract on the other. I am firmly convinced that cholecstectomy should be done whenever cholelithiasis is found, in order to prevent liver damage. Certainly the morbidity and mortality of operative intervention can be markedly decreased if such operations are done before liver damage supervenes or when the liver damage has been improved by the therapeutic measures outlined above. This matter should be seriously considered unless there is a definite contraindication for operative interference. In my experience contraindications become fewer when a scientific evaluation of a surgical risk is made and scientific management substituted for the haphazard surgical procedures commonly employed.

The patient suffering from severe liver disease is in danger of hepatic failure and coma. Here intensive treatment with dextrose intravenously and with plasma, liver extract and vitamins may be life saving. Oxygen therapy is necessary with these measures, to combat the hepatotoxic effects of anoxemia. Oxygen is best given in an oxygen tent. Nasal catheters are contraindicated because pressure necrosis from the rubber may result from a possible uremic state, which can form a part of the clinical picture. I have seen severe pharyngitis and erosions of the nose with subsequent bleeding follow the use of rubber tubes in the nose and mouth.

Under special conditions certain other agents are of value in the treatment of liver disease. These include lipocaic, bile salts and various fractions of the vitamin B complex.

Of the complications that occur during jaundice, acute hepatic insufficiency and hemorrhage are the most important. Both are discussed in this chapter, and no repetition is necessary here. Finally, the whole therapeutic approach to this problem should be controlled by repeated laboratory investigations, which would indicate the improvement, if any, that has taken place in the liver as the result of the treatment outlined. I cannot urge too strongly the need for a conservative and scientific approach to the problem of treating jaundice. One should not be too eager to operate just because of the presence of bilirubinemia, and one should not prolong operation in a patient with a definite surgical type of jaundice. There is no substitute for keen clinical judgment in this disease.

After the jaundice has disappeared and definite clinical improvement has been noted in patients disabled by liver disease, ambulatory management should be continued for many months, until repeated liver function tests indicate restoration to normal. When this has been brought about, the patient should be warned against exposing himself to the same etiologic factors that brought about the original condition.

I am sure that the reader will infer from what has been said above that we can no longer look on a patient with liver disease as in a hopeless state. Even patients with marked ascites, when the liver damage is not irreversible, can be brought back to a near-normal existence if the procedures that have been described will be carefully followed. There is no more gratifying experience to the clinician than the therapeutic results obtained in the scientific handling of patients with liver disease.

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METABOLIC DISEASES OF THE LIVER

Since the liver is active in metabolism, it is obvious that all hepatic disorders will affect the metabolism of the liver tissue and of the entire body, but in certain conditions that are primarily disorders of metabolism, the hepatic changes are of especial importance.

Hepatomegaly in Diabetes Mellitus.—This disorder complicates diabetes mellitus in children especially, but also occurs occasionally in elderly patients. The hepatomegaly generally results from fatty infiltration of the liver because of the malnutrition associated with poorly controlled diabetes mellitus. In some cases the enlargement of the liver is the result of edematous changes in the hepatic parenchyma. There usually are no specific symptoms, but the liver is enlarged in varying degrees. Sphenomegaly may or may not be present. Abdominal pain frequently accompanies the hepatomegaly, presumably because of stretching of the hepatic capsule. The hepatomegaly in diabetes mellitus may result from various complications of diabetes. It may result from the malnutrition associated with poorly controlled diabetes mellitus or from acute hepatitis of any cause complicating the diabetes. The effect of the hepatomegaly on the diabetes varies with the exciting cause; usually the hyperglycemia and glycosuria are aggravated, and ketosis becomes frequent. In most cases the hepatomegaly is alleviated by improved control of the diabetes mellitus with insulin and diet, and the hepatic lesions usually are completely resolved. Lipocaic, the fat "hormone" of the pancreas, also has been used successfully in treatment in some cases.

The Cholecystohepatohyperglycemic and Glycosuric Syndrome.—Cholecystitis and cholelithiasis tend to produce liver damage that may become severe. Occasionally with long-standing gallbladder disease, interspersed with attacks of acute or subacute cholecystitis, there will be persistent hyperglycemia and glycosuria. I described 6 cases of this association recently. Essentially the condition is the result of an increased rate of liberation of dextrose to the blood by the liver, probably because an abnormal amylase breakdown of liver glycogen is operating in the damaged liver. Usually there is a long history of gallbladder attacks, and glycosuria is present. Ketone bodies are not found in the urine, and attacks of diabetic acidosis rarely occur. The signs of a diseased gallbladder usually are present, and the gallbladder is not visualized. The blood sugar concentration may be as high as 250 mg. per hundred cubic centimeters, but in spite of what seems to be an adequate amount of insulin and a strict dietary regimen, the patient continues to show hyperglycemia and glycosuria. The dextrose tolerance curve is that of liver disease rather than that of diabetes mellitus.

Actually, insulin treatment drives glycogen out of the liver and puts it into the muscles as glycogen, so that the insulin increases the glycogenolytic process in the liver. The lowered amount of liver glycogen favors increased liver damage. Hyperglycemia induced by intravenous dextrose therapy inhibits the glycogenolysis; the liver stores more glycogen, and the blood sugar level tends to fall. In some cases, cholecystectomy and pre- and postoperative dextrose therapy produce, along with the improvement in glycogen storage in the liver, an improvement in the other liver functions and a return of the blood sugar level nearly to normal. No sugar is ever found in the urine again, although no insulin is used at any time.

Von Gierke's Disease.—Von Gierke's disease, the glycogen storage disease, usually is characterized by hepatomegaly. This condition depends on an excessive accumulation of glycogen in many organs, because of an abnormal stability of the tissue glycogen. Probably there is usually an inactivation or an absence of some of the normal intravellular enzymes that bring about glycogenolysis. The liver is greatly enlarged, and the hepatic cells are packed with glycogen. The glycogen level does not decrease rapidly, as it usually does when the liver tissue is allowed to stand in a test tube for several minutes or hours. The addition of amylase or of extracts of normal liver tissue (containing glycogenases) causes a rapid disappearance of the glycogen, emphasizing the fact that there is a lack of enzymes active in causing glycogenolysis. Clinically, there are hepatomegaly without splenomegaly and hypoglycemia with ketosis before breakfast. The hypoglycemia results from the inability of the liver to liberate dextrose to the blood as rapidly as normal, while the ketosis is the result of the compensatory increase in the fat metabolism. The heart also may be involved by the glycogen storage disease, and the patient often shows symptoms of cardiac failure and cardiac enlargement as a consequence. Occasionally the pylorus is affected by the glycogen storage process, and symptoms of pyloric obstruction occur. There is markedly decreased resistance to infections and toxemias. Treatment is aimed at the relief of hypoglycemia and ketosis by frequent small feedings of carbohydrate and at protecting the patient against infections. The possibility of alleviating the defective glycogenolysis by the use of certain hormones or enzymes as yet is in the experimental stage.

Gaucher's Disease.—This condition is caused by a disturbance in the cerebroside metabolism, with a resultant accumulation of cerebrosides in the reticuloendothelial cells. Clinically, there are marked hepatomegaly and sphenomegaly, with irregular pigmentation of the skin and yellowish wedge-shaped conjunctival thickenings near the cornea. There may be hemorrhagic diathesis, probably resulting from involvement of the bone marrow. Areas of decalcification may be seen in the bones, with some deformity and irregular growth. Gaucher's foam cells containing cerebrosides may be seen on examination of tissue obtained by sternal or splenic puncture. Treatment consists of irradiation of the lesions in the bones and spleen. Splenectomy may be necessary when the spleen is markedly enlarged. Periods of exacerbation and remission alternate, and death usually occurs within several years.

Niemann-Pick Disease.—This lipoid storage disease is even more uncommon than Gaucher's disease. In this condition, the histiocytes and the reticuloendothelial cells are filled with phosphatides. The spleen, liver, lymph nodes and bone marrow are involved, as in Gaucher's disease, as well as the adrenal glands, thymus, lungs and kidneys. The epithelial cells of many organs also may contain the phosphatides. The condition is a familial disease and is found chiefly in Jewish infants. The outstanding symptom is abdominal distention caused by the marked splenomegaly and hepatomegaly. Death occurs before the third year of life in most cases, and treatment is restricted to symptomatic measures.

Xanthomatosis.—In Schüller-Christian disease, there are nodular deposits of cholesterol and cholesterol esters in fibrous tissues, especially in the periosteum of bones and in the dura mater. The periosteal deposits cause bone erosions, especially in the membranous bones of the skull, and deposits in the ocular orbits may result in exophthalmos. Frequently also deposits of cholesterol near the pituitary gland result in diabetes insipidus or in pituitary dwarfism. Hepatic and splenic lesions are not particularly common.

In the lipoidosis of Bürger and Grütz, however, hepatomegaly and splenomegaly are present, with marked hyperlipemia, an eruptive cutaneous xanthoma and an increase in the phospholipids of the blood and tissues. There are large accumulations of xanthoma cells in the liver, and usually cirrhosis of the liver is present.

Xanthomatous cells may accumulate in the liver in various conditions associated with prolonged hyperlipemia, *e. g.*, diabetes mellitus. In all these conditions as well as those previously mentioned, there are groups of xanthoma cells in the liver, cirrhotic lesions and some biliary obstruction, often caused by accumulations of xanthoma cells in the walls of the bile ducts. Jaundice frequently precedes the appearance of cutaneous xanthomas, the latter usually becoming apparent during the course of the jaundice or shortly thereafter. Treatment of the liver damage usually has some beneficial effect on the xanthomatosis also, but a curative therapy for the latter is not yet available.

INFECTIOUS DISEASES OF THE LIVER

The liver is subject to certain infectious conditions, some of them peculiar to it. In all these, the liver functions are markedly impaired, frequently so severely that hepatic coma and death ensue.

Suppurative Pylephlebitis.—Infection of the portal vein by pyogenic organisms is most frequently encountered as a result of acute appendicitis. It may also result from suppurative cholangitis dysentery, colonic neoplasms, prostatic abscesses and tuboövarian abscesses. Usually the infective processes are limited to either intrahepatic or extrahepatic branches of the portal vein. The wall of the portal vein is inflamed, and blood and pus may ooze into the surrounding tissues. Usually the liver enlarges and may show many focal abscesses scattered along the course of the branches of the portal vein. The spleen frequently is enlarged and "septic." Chills and septic fever characterize each new extension of the infective process. A single chill may signify that a single local phlebitis of one branch of the portal vein has occurred. Mild hepatocellular jaundice frequently occurs, as does palpable hepatomegaly. Palpable splenomegaly is not common, although the spleen is generally large. Vomiting is almost invariably present. Usually the infection is fatal, generally because of septicemia and occasionally because of hepatic failure. However, recovery may occur spontaneously, or after drainage of the liver abscesses that result from the portal phlebitis. Sulfonamide and penicillin should be used to prevent spread of the infection.

Pyogenic Liver Abscess.—Pyogenic liver abscesses result from extension of nearby suppurative lesions in the gallbladder, peritoneum or pleura and from hematogenous infection by suppurative pylephlebitis or by entrance of infected emboli through the hepatic artery. Penetrating wounds, such as bullet or stab wounds, also may result in liver abscesses. The organisms involved in the production of these abscesses are chiefly the staphylococci, streptococci, *Bacillus coli*, Friedländer's bacilli and dysentery bacilli. The abscesses may be multiple or solitary. The right lobe usually is more affected by liver abscesses than the left.

In most cases the liver abscess is merely a complication of a serious disease, and appears with chills, increase in fever and local pain. Symptoms may disappear when the abscess becomes encapsulated. Fever, pain, nausea, vomiting, signs of liver failure and hepatomegaly are most often encountered. Tenderness over the liver, fluoroscopic evidence of limitation of the excursions of the diaphragm near the abscess and loss of weight and cachexia are characteristic. The abscess may perforate through the diaphragm into the pleural space or lung, or it may rupture into the peritoneum and cause peritonitis. Subphrenic abscess is frequently the result of rupture of a liver abscess. Treatment with sulfonamides or other antibacterial agents to limit the spread of the infection and incision and drainage to remove the pus are necessary. Exploratory aspiration with a syringe and needle is sometimes attempted, but the procedure is dangerous and usually is inferior to operation.

"Catarrhal Jaundice" (Acute Infectious Hepatitis).—Catarrhal jaundice no longer is believed to result from catarrhal inflammation of the bile passages and from edema and congestion of their mucous membranes. In most cases there is an acute infectious hepatitis in which the hepatic parenchyma shows many toxic and degenerative changes, with inflammatory cellular infiltration of the hepatic connective tissue. Catarrhal jaundice, therefore, may well be called an acute yellow atrophy in milder form.

Rarely the catarrhal jaundice may actually be the result of mild inflammation causing swelling at the opening of the common bile duct into the duodenum (duodenitis) or obstruction of the common bile duct by mucous plugs. It is probable that the term includes a large number of separate conditions. Infectious hepatitis frequently occurs in epidemics, and usually such epidemics are associated with epidemics of gastrointestinal disease or of respiratory infections. Several different organisms have been isolated by various investigators during different epidemics; among them are dysentery and paratyphoid bacilli. Most investigators, however, have been unable to identify any specific bacterial cause of epidemic hepatitis. In recent years a search has been made for an ultrafiltrable virus as the cause of several such epidemics. Transmission of such a virus through pigs as a vector has been suggested also. A search has been instituted for a virus transmitted by human blood serum, after reactions to yellow fever vaccine resembling mild acute yellow atrophy were traced to icterogenic human blood serum. Sometimes hepatitis following inoculation with icterogenic human serum comes on after a long incubation period, amounting to as much as six months. On the other hand, certain unknown noninfectious icterogenic factors may occur in human blood serum to cause the epidemics of hepatitis after vaccination with products containing blood serum or after blood transfusions. Infectious hepatitis associated with epidemics of respiratory infection often shows characteristics of infectious mononucleosis. The causative organisms of this disease and of the frequent sporadic catarrhal jaundice are unknown. Catarrhal jaundice may, in fact, follow many unrelated infections.

Usually catarrhal jaundice is considered to be a mild diseale, but it may present all stages of hepatitis from a mild hepatocellular and obstructive jaundice to outright acute yellow atrophy of the liver that terminates in hepatic coma and death. The disease generally occurs in young adult patients, and the first symptoms usually are gastrointestinal: anorexia, nausea, vomiting, epigastric discomfort and tenderness in the upper part of the abdomen. The patient complains of general malaise and fever, and physical examination shows the liver somewhat enlarged and tender and the spleen possibly palpable. After several days the temperature approaches normal, and jaundice of variable degree appears. The malaise and anorexia remain, but the epigastric discomfort tends to disappear, usually with the onset of jaundice.

In all phases of the disease, liver function tests will show some impairment. Early there may be what is called an "obstructive" phase, in which there is acholuric jaundice, with light colored stools and little urobilinogen in the urine. This is followed by a phase in which more bile is discharged into the intestine, the stools become pigmented once more, and the urobilinogen excretion in the urine may be increased. After this comes convalescence, with improvement in the liver functions. In this last phase the liver function tests all tend to return toward normal; the serum bilirubin concentration decreases toward normal, and the patient improves clinically. The leukocyte count in active catarrhal jaundice is usually normal, slightly decreased or slightly increased. There is definite neutropenia and a relative or absolute lymphocytosis. Frequently there is monocytosis.

The jaundice usually disappears within about three weeks, leaving the patient feeling well or slightly weak. For weeks after the jaundice has disappeared the patient tires easily, and usually impairment in liver function continues for years after supposed recovery. The patient should be examined and watched carefully for liver damage, and prompt treatment is essential to prevent serious complicating infections, to which the patient has little resistance. The treatment of catarrhal jaundice is the same as the treatment of liver damage from other causes.

Syphilis of the Liver.—This liver is involved in practically every case of congenital syphilis, but the clinical picture rarely is predominantly that of liver disease. The liver shows swarms of spirochetes usually and is greatly enlarged. There is an increase in the hepatic connective tissue, and the architecture of the lobules is changes or becomes irregular. Areas of necrosis and leukocyte infiltration are frequent, and some giant cells are present.

The hepatic disorders in acquired syphilis are different in early and late stages. The incidence of clinical liver disease caused by syphilis is given by different authorities as from 0.05 to 2 per cent of cases of syphilis.

In early syphilis, there may be acute hepatitis characterized by hepatocellular jaundice, fever, malaise, nausea, vomiting and hepatomegaly. Usually the clinical manifestations of the hepatitis last about one month. The hepatitis may become severe enough to result in acute or subacute yellow atrophy of the liver, terminating in cholemia and death. The milder form of hepatitis usually disappears rapidly under antisyphilitic therapy and treatment for liver disease.

In the late stages of syphilis, there may be acute hepatitis, but usually there are hepatic gummas, which are laid down in the liver and go on to necrosis. Healing follows, with replacement by fibrous tissue and compensatory hyperplasia of the uninvolved areas of the liver. Parenchymal atrophy and contraction of the fibrous tissue bring about deep cicatricial lesions and marked deforming lesions of the liver (hepar lobatum).

The symptoms may resemble those of other types of acute hepatitis or, more usually, those of cirrhosis. The enlarged, irregularly nodular liver (hepar lobatum) is usually easily palpated. The treatment consists of the usual measures for the treatment of hepatitis and cirrhosis, with antisyphilitic therapy with bismuth and iodides. The use of the arsphenamines in the presence of hepatic disease is discouraged unless other considerations make it necessary. These drugs occasionally themselves cause a toxic hepatitis, characterized by parenchymal degeneration, necrosis, cholangitis and sometimes acute yellow atrophy. It is possible that in some cases arsphenamine jaundice is caused primarily by obstructive lesions of the intrahepatic biliary tract rather than by parenchymal damage.

Tuberculosis and Liver Disease.—Frequently with pulmonary tuberculosis there will be a tubercle of the liver, but clinical liver disease is less common. Miliary tuberculosis of the liver occurs occasionally by transmission through the hepatic artery or the portal vein from other foci. More common are the fatty changes and demonstration of impairment on liver function tests, even when pulmonary tuberculosis is mild. The febrile and toxic characteristics of tuberculosis and the associated disturbances in the nutritional balance are probably responsible for these changes.

NEOPLASTIC DISEASE OF THE LIVER

Neoplastic diseases of the liver include benign neoplasms such as adenoma of the hepatic parenchyma or of the intrahepatic bile duct epithelium, fibroma and lipoma. They are uncommon and usually unimportant clinically. Malignant disease of the liver is commonly secondary to disease elsewhere. Sarcoma is usually secondary.

Primary Carcinoma of the Liver.—Primary hepatic carcinoma occurs most often in middle-aged persons who are suffering from cirrhosis, which definitely aids in the development of the carcinoma. Primary carcinoma of the liver is rare in the United States, but is found frequently in regions where parasitic liver disease and malnutrition are more common, namely, China and South Africa. Certain toxic substances cause cirrhotic lesions and if exposure is continued long enough, may cause neoplastic change in the hepatic cells. Dibenzanthracene and methylcholanthrene, among others, are widely used to produce hepatoma in experimental animals. Some of these substances are encountered in industrial processes, and effective precautions against hepatic damage should be the rule where this is true.

Hepatic carcinomas include the hepatoma, arising from the hepatic epithelium, and the cholangioma, from the epithelium of the intrahepatic bile ducts. The hepatoma is about five times more common than the cholangioma. Hepatoma may consist of one large tumor and several smaller ones or many small tumors in the liver (both types multicentric). Necrosis and hemorrhage frequently occur in the nodules or carcinomatous masses. The histologic picture is of anaplastic hepatic cells capable of forming bile even in some of the metastases. Amitosis frequently causes the formation of giant multinucleated cells. Cholangioma is less often associated with cirrhosis, but forms multiple adenocarcinomatous nodules throughout the liver. The carcinoma cells are cuboidal or columnar, showing no secretion of bile, and there is more fibrous tissue than in the hepatoma. The liver, however, is stained with bile because of obstruction of the normal biliary passages. There may be a transition form between hepatoma and cholangioma.

Secondary Carcinoma of the Liver.—Secondary carcinoma is seen about twenty or thirty times as often as is primary carcinoma of the liver. Usually the lesions are metastases from the gastrointestinal or from the pelvic organs. The stomach is the most frequent primary site of the neoplasm, but cancer of the breast and lung also frequently send metastases to the liver. The liver may be of normal size or greatly enlarged. The tumors usually are multiple, and more are present on the surface than deep in the liver. The tumor nodules vary in size and show areas of necrosis and hemorrhage. Those at the surface usually show a dimpling (umbilication) of their centers, because of necrosis of the center.

Symptoms of Hepatic Neoplasm.—Usually with primary neoplasm the chief complaint is of the symptoms of cirrhosis, since that disorder is generally coexistent. The cirrhosis appears to progress rapidly, with an inordinate amount of weakness; rapid appearance of ascites, frequently hemorrhagic, and jaundice in about 50 per cent of the cases. Upper abdominal pain is more frequent than in simple cirrhosis and usually is caused by perihepatitis. An unexplained mild fever also is frequent.

Hepatomegaly generally exists, but sometimes the enlargement is upward, elevating the diaphragm, and is not apparent on palpation, when mensuration of the thickness of the liver by percussion or x-ray examination gives more accurate results. Tenderness over the liver also is more frequent than in simple cirrhosis because of the greater frequency of perihepatitis with carcinoma. A palpable spleen is found only rarely. The tumor nodule may be palpable, and occasionally it may be possible to palpate the umbilication of the secondary neoplastic nodules. Palpation is done more easily when the abdominal wall is flaccid, after the drainage of ascitic fluid by paracentesis. Usually the downhill course of the disease is rapid, and signs of hepatic coma may set in before death is caused by cardiovascular or infectious disease. Diagnosis by palpation of the tumor nodule in the absence of splenomegaly may be confirmed by roentgenologic visualization of the liver, in which tumors appear as areas of reduced density in the outline of the liver, and by peritoneoscopy or exploratory laparotomy. The presumptive diagnosis of metastatic neoplasm of the liver may be simplified when it is known that the patient is suffering from a primary carcinoma of another abdominal organ.

Treatment.—Only rarely can surgical resection be done early enough to remove all of a neoplasm of the liver, whether it be primary or secondary. Usually only symptomatic therapy and palliative irradiation of the liver can be utilized.

ACUTE YELLOW ATROPHY

Acute yellow atrophy is an acute diffuse necrosis of the liver cells, resulting from intoxication or infection. It is characterized by a progressive diminution in the size of the organ and profound toxemia. It occurs most frequently between the tenth and the fortieth year of life; about 50 per cent of patients are between the ages of twenty and thirty years. It occasionally occurs in children.

The etiology of the condition is still obscure. In women the most common cause is pregnancy. Infectious diseases, such as syphilis, malaria, typhoid fever, diphtheria, influenza, appendicitis, osteomyelitis and erysipelas, frequently precede this condition. Such microörganisms as colon bacilli and some of the cocci have been found in the liver. However, in all probability these are secondary invaders. Of the toxic agents, arsphenamine, employed in the treatment of syphilis, is the most frequent causative agent. There seems to be some disagreement among authorities as to whether patients treated by this means are more disposed to the disease than nonsyphilitic patients. However, Lindstedt[1] found, in studying the histories of 9,696 patients from different countries, that jaundice attacks patients treated with arsphenamine much more frequently than others. From this one may conclude that arsphenamine therapy for the syphilitic patient is a predisposing factor. Such agents as alcohol, chloroform, phosphorus, ether and, more recently, trinitrotoluene, carbon tetrachloride, trichlorethane, dinitrophenol and cinchophen and its various preparations are also factors in producing this disease. Lately sulfanilamide has been added to this list.

The literature on the frequency of changes in the liver following cinchophen therapy is increasing. However, it seems justifiable to conclude from the widespread use of cinchophen and the infrequency of jaundice occurring during its administration that the normal liver may not be susceptible to cinchophen, whereas a predisposed diseased liver may be the important factor in the development of acute yellow atrophy. Parenthetically, therefore, a note of warning should be given as so the indiscriminate use of cinchophen for patients who have a diseased liver.

Several theories have been brought forward to explain the exciting cause of acute yellow atrophy. Since the disease frequently follows other hepatic disorders, it may be not a definite entity in itself but just the end-result of a toxic hepatitis. Flexner promulgated the theory that the process is autolytic and is produced by a toxin with a specific action on the liver cells, destroying them without injuring the proteolytic ferments that the latter contain. Opie[2] presented the theory that it is the result of disturbances of metabolism.

Morbid Anatomy.—The liver is greatly diminished in size, and the surface is shrunken and wrinkled. The atrophy is more advanced, as a rule, in the left lobe. The color is yellowish green and sometimes dark red. On section, the liver is yellowish and contains scattered depressed areas of reddish color (red atrophy). When the atrophy is subacute, raised areas of yellowish or greenish color, which are due to compensatory regeneration, may be seen. The markings of the lobules are indistinct, particularly in the red areas. The liver tissue is soft and friable. The bile ducts contain mucus, and the gallbladder may either be empty or contain a small amount of bile.

Microscopically, there is widespread degeneration of the liver cells, which makes the architecture difficult to recognize. This is particularly true in the reddish areas, and the cells usually show all stages of necrosis. First they become granular and bile stained, and later fragmentary degeneration takes place in the nuclei, which soon lose their staining power. The cells around the central veins appear to undergo complete destruction, and only debris and the fibrous and vascular framework of the organ may be seen. Hemorrhages between the liver cells are not uncommon.

In the subacute phase the surviving liver cells at the periphery of the affected areas and the cells of the intralobular bile capillaries show evidence of compensatory regeneration. This regeneration of the liver cells in the formation of areas or nodules stands out from the surrounding shrunken tissue. If the disease does not rapidly prove fatal, fibrotic changes take place in the interstitial tissue. At the same time, the spleen may be enlarged; the epithelium of the kidneys may undergo granular degeneration, and the myocardium may become softened.

Symptoms.—The initial stage resembles that of an ordinary catarrhal jaundice, and the symptoms may be very mild, lasting from a few days to two or three weeks. After this the second stage sets in abruptly, with severe headache, restlessness,[4] delirium, vomiting, convulsions, transient paralysis and dilatation of the pupils. These are among the prominent features and are indicative of marked toxemia and irritation of the nervous system. Jaundice, which may be absent when progress is extremely rapid, may produce a dark yellow or bronzelike yellow and slightly greenish color. Hemorrhages into the skin or from the mucous surfaces may occur. The bleeding tendency is probably caused by prothrombinopenia or occasionally by lowered blood fibrinogen. This is a result of liver failure, since parenteral injection of vitamin K does not improve the blood prothrombin level. The temperature usually remains low but may rise suddenly before death. The disease proves fatal a few days after the onset of the severe symptoms, usually after the development of coma and stertorous breathing.

The liver begins to diminish in size with the onset of the second stage. It is flabby, tends to fall away from the abdominal wall and is replaced by coils of the intestine; therefore it is extremely difficult to ascertain the size of the liver by percussion, because of tympany in the hepatic region. The spleen is usually enlarged. The urine, which is scanty, becomes markedly bile stained and contains albumin and casts. The quantity of urea is diminished, and the ammonia nitrogen content increased, probably the result either of the failure of the liver to convert the ammonium compounds into urea or of acidosis and the fixation of ammonia by organic acids. Leucine and tyrosine crystals are usually present. The coagulation time of the blood is generally prolonged, and there may be a moderate leukocytosis.

Diagnosis.—In the absence of obstruction the diagnosis of acute yellow atrophy may be made on the basis of the acute and sudden occurrence of jaundice, the progressive diminution in the size of the liver, the development of severe nervous manifestations and the dilatation of the pupils. Difficulty in differentiating the condition from catarrhal jaundice may be experienced in its early stages. However, it must be emphasized that when jaundice appears in pregnant women it should not be looked on lightly, particularly if enlargement and tenderness of the liver are evident, as it may be indicative of a more severe condition. The line of demarcation between the clinical picture of acute yellow atrophy and that of less violent involvement is less distinct than has been supposed.

The urinary changes, especially evidence of acid intoxication, are of diagnostic importance, and their timely detection may prevent more serious development of the disease. The characteristic signs in the more advanced stages include jaundice, vomiting, delirium and other nervous (cerebral) symptoms, diminution in the size of the liver and the presence of leucine and tyrosine in the urine. It must, however, be emphasized that the finding of these aminoacids in the urine is not of conclusive diagnostic value, since they are also present with several other diseases, such as afebrile jaundice with slight enlargement of the liver, leukemia, erysipelas and typhoid fever. With catarrhal jaundice the pulse is usually slow; whereas with acute yellow atrophy it is increased. Some other characteristics of differential value from catarrhal jaundice are the increasing languor or irritability ending in cholemia, decreasing size of the liver, tendency to hemorrhages, a tendency to anasarca (because of hypoproteinemia) and increased red cell sedimentation rate with increasing hyperbilirubinemia, decreasing cholesterol esters and increasing blood aminoacids. The direct van den Bergh reaction is more significant in cases of acute yellow atrophy than of catarrhal jaundice.

Prognosis.—The disease usually proves fatal in about two weeks. In a small percentage of cases a subacute stage develops, which may last from six to eight weeks. When the symptoms become mild, or if they abate, ultimate recovery may be anticipated. However, the disorder becomes chronic and usually terminates fatally. The prognosis virtually depends on the severity and length of the second stage of the disease. In pregnant women the prognosis is invariably bad.

Treatment.—The treatment of acute yellow atrophy resolves itself into preventive and symptomatic treatment. Rolleston[3] suggested that as a prophylactic measure chloroform should never be given to jaundiced pregnant women and that mercury should be used in treating the benign jaundice of early syphilis. It arsphenamine is administered in the treatment of syphilis, the blood ought to be examined regularly for early evidence of hyperbilirubinemia. Other tests should be employed from time to time to determine the state of liver function. If jaundice appears during pregnancy, it may be the forerunner of acute necrosis of the liver. The urine should be carefully studied for evidences of acid intoxication. For acute hepatic insufficiency the treatment outlined for severe liver damage is the important approach. It must be emphasized here that intravenous administration of dextrose is the method *par excellence* of administering carbohydrates. The diet should be rich in carbohydrates but deficient in fats. Some authors have advised transduodenal drainage as a method of removing the toxic substances in the bile. The chloride balance should be carefully watched, and the chloride loss should be made up by intravenous administration of chlorides, possibly in the form of 100 to 200 cubic centimeters of a 2 per cent solution of sodium chloride. The most important factors in all the treatment are watchful expectancy and careful evaluation of the clinical and the laboratory picture of the patient during the course of the disease.

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LIVER DEATHS

Death as a result of liver failure is of uncertain incidence, and the mechanism is as yet unexplained. In 1922 Heyd[2] described the liver death syndrome that occasionally follows biliary tract operations, and since then three types of postoperative liver death have been recognized. In the first group there is a slow emergence from the anesthesia, and hyperpyrexia, coma and death follow in eighteen to thirty-six hours. In the second group are cases of obstructive jaundice; stupor and coma follow operation by four to seven days in these; there is hyperpyrexia, and death occurs in coma. In the third group are cases of what is known as the hepatorenal syndrome; vasomotor collapse and progressively increasing oliguria and azotemia appear about forty-eight hours after operation; there is no hyperpyrexia. Similar liver deaths may appear after almost any type of surgical procedure, after trauma to the liver in the presence of thyrotoxicosis, intestinal obstruction or burns.

In any severe parenchymatous liver disease hepatic coma[3] or cholemia may appear as the terminal stage of the disease. In this condition restlessness and anxiety, fever of variable degree, abdominal pain and oliguria are early symptoms. Somnolence or disorientation and acute delirium are frequent, and in twenty-four to forty-eight hours a deep coma develops.

A variable degree of spasticity and often ankle clonus and positive Babinski reflexes may develop before the coma. Convulsions appear occasionally, usually in children, in whom there may also develop a characteristic "cholemic shrieking."

In these cases, liver function tests show marked abnormality. Usually there is a progressive increase in blood aminoacid nitrogen, polypeptid nitrogen, ammonia and "rest" nitrogen, and later some hypochloremia may occur. The pyruvic and lactic acid levels of the blood may increase in the later stages, and in the terminal stages acidosis may supervene. Hypoglycemia is rare.

The mechanism of the medical hepatic coma, according to Snell and Butt,[3] may be a biochemical lesion involving a breakdown of enzyme systems concerned in the intermediary metabolism of carbohydrates. These authors developed a therapeutic regimen using large amounts of intravenous dextrose with thiamin and niacin and reported promising results. They expressed the belief that this type of hepatic coma differs definitely from the postoperative type.

Boyce[1] suggested that underlying postoperative liver death is hepatic damage, increased by the strain of operation and anesthesia. The damaged liver cells release a toxin that is excreted by the kidneys, but the renal tubules are damaged in the process and break down.

If the process is fulminating, the early death with hyperpyrexia of Group 1 results. If the process is less severe and the elaboration of hepatic toxins less rapid, the patient survives long enough for the destruction of renal parenchyma and death to occur as in Group 2 or 3. The mechanism of the hyperpyrexia is still not definitely known.

Recognition of the preëxisting hepatic insufficiency by routine use of reliable liver function tests is recommended, to make possible proper preoperative preparation of the liver for any operation and to avoid precipitating liver failure. For the medical hepatic coma, intensive intravenous treatment with dextrose, minerals and fluids and the use of large amounts of thiamin, niacinamide and liver extract are promising.[3]

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CHAPTER XIX

GALLBLADDER DISEASE

ETIOLOGY

Cholecystitis.—Cholecystitis is either acute or chronic, but in both instances the inflammatory process is due to bacteria, and there is marked difference as to the type of bacteria and the route of infection.

Boyd[6] stated that the bacteria found in chronic cholecystitis are in most instances the nonhemolytic streptococcus viridans, low in virulence; he called attention to the fact that these organisms are found in the gallbladder and not in the bile, as the latter exerts an inhibitory influence on them. Williams and McLachlan,[39] after a careful study, reported that they found *Bacillus coli* in 20 per cent of cases, but streptococci in only 16 per cent, and that in the cases of streptococci involvement the bile was frequently infected; furthermore, staphylococci and typhoid bacilli were occasionally noted. They expressed the belief that in acute cholecystitis, especially in the fulminating type, *Bacillus welchii* and other anaërobic organisms may be the principal infecting agents, and it is entirely possible that these bacilli may come from the liver.

Gordon-Taylor and Whitby[15] found the bacillus welchii in 9 per cent of gallbladders removed surgically, and in 13 per cent of gallstones removed post mortem.

It is generally accepted that infection occurs through the blood stream and from the liver and not by ascent from the duodenum. Authorities are agreed that hematogenous infection is usual and claim that the inflammatory lesions of chronic cholecystitis are most marked in the deeper part of the wall. Wilkie[37] recently stated that streptococci are more readily cultured from the outer layers than from the mucosa, his explanation being that this is due to the inhibitory action of the bile. Animal experiments undertaken by Wilkie to prove his assertion were considered by him confirmatory, but similar studies reported by Williams and McLachlan failed to verify his results.

There are two ways in which hepatogenous infection may occur: 1. If the bacteria which are carried to the liver by the portal vein from the bowel are not destroyed they are excreted in the bile and may infect the gallbladder. The infective foci are usually localized in the outer part of the wall, and this would seem to eliminate the idea of an infection of the mucous membrane. 2. Evarts Graham has suggested that the infection may progress from the liver to the gallbladder *via* the lymphatic vessels. Hepatitis is frequently found in the neighborhood of an inflamed gallbladder, and one must remember that the infection may have spread from the gallbladder to the liver.

Andrews, Schoenheimer and Hrdina[1] claimed that ligation of the cystic or the common bile duct produces biliary stasis, favoring prompt infection of the gallbladder wall by anaërobic organisms which appear to pass from the liver to the gallbladder by direct extension.

It would be a mistake to consider that the methods of infection described are essentially exclusive, for the infection in one case may be by the lymphatic vessels from the liver and in another by the blood stream; at times it may be spread by the bile.

The state of the gallbladder depends on the degree and virulence of the infection. If acute, it may well be suppurative; on the other hand, it may be chronic, and as has often been stated, the chronic state may not necessarily be preceded by an acute attack.

While cholecystitis is frequently associated with gallstones, it is possible for this condition to occur without them. MacCarty[21] called attention to the fact that of 365 cases of cholecystitis there were stones in 69 per cent with acute catarrh, in 76 per cent with chronic catarrh and in 93 per cent with advanced chronic inflammation.

Boyd's[5] description of the pathology of *acute and chronic cholecystitis* is so remarkably clear and comprehensive, so concise and yet so adequate, that I shall refer the reader to his paper in this regard.

Lipoid Gallbladder.—An interesting pathologic state is the lipoid gallbladder, often referred to as the strawberry gallbladder, which is characterized by deposits of small yellow specks on the reddened mucosa; the whole surface or only isolated portions may be involved.

The material noted presents certain characteristics of neutral fat, but when stained it becomes different; this substance is soluble in alcohol and chloroform; it stains red with scarlet red and black with osmic acid. It is thought that the condition is produced by two factors, an increase in the bile cholesterol and mild chronic inflammation.

The amount of cholesterol in the bile bears a distinct relation to the amount in the blood, and the cholesterol of the bile is absorbed through the epithelium lining the gallbladder. After intensive investigations, Elman and Graham[13] concluded that it is excreted instead of absorbed by the gallbladder and that inflammation accelerates the excretion; they stated it as their firm conviction that infection is the factor of major importance in the pathogenesis of the "strawberry gallbladder." Blaisdell and Chandler,[4] after a study of the subject, concluded that the deposits were the result of absorption, while Patey[24] found that tying the cystic duct during a cholesterol feeding investigation did not interfere with the formation of cholesterol deposits in the gallbladder wall. Theories are contradictory, but the results obtained by Wilkie and Doubilet[38] appear the most likely to be near the truth. They showed that the direction of the passage of cholesterol through the gallbladder wall depends on the blood-bile cholesterol ratio; that is, when the cholesterol concentration of the bile is lower than that of the blood, cholesterol passes from the blood through the gallbladder mucosa into the bile; when it is higher, the passage is in the opposite direction.

Undoubtedly infection plays a direct role in this condition, but in exactly what manner is not definitely understood. It has been suggested that infection either causes precipitation of the cholesterol in the tissues or converts it from an invisible into a visible form; or the reaction may occur in the absence of inflammatory change.

Stasis Gallbladder.—Many outstanding authorities, including Aschoff, Berg and Westphal, have been interested in the so-called stasis gallbladder, with which at operation a patient who had presented symptoms of gallbladder disease shows neither cholecystitis nor cholelithiasis. Two varieties of gallbladder presenting a stasis of bile with a tendency to gallstone formation have been described, atonic and hypertonic, the former being of the thin, relaxed type, while the latter is rather thick and distended. Westphal expressed the opinion that the hypertonic type is the result of vagal spasm of the neck of the gallbladder and the sphincter of Oddi, a condition frequently present in the early months of pregnancy. Obviously, then, such a state may be of importance in bringing about the formation of gallstones in pregnant women. Gerdes and Boyden[14] concluded that in the second and third trimesters of pregnancy the emptying of the gallbladder is markedly retarded during the first part of a phase of contraction induced by the most potent food known for activation of the gallbladder musculature. It inevitably follows from this that the biliary vesicle must accumulate stagnant bile during the period of gestation, the degree of stasis varying with the individual. They called attention to the confirmation of this fact by Potter,[27] who stated that he observed in 390 cesarean sections at term that approximately 75 per cent of the patients, supposedly healthy women, had a large, globular, distended gallbladder, and that analysis of the contents of the biliary vesicle, withdrawn through a sterile needle at the time of section in 58 cases, showed a raised cholesterol and surprisingly low bile salt concentration, the latter being comparable to that found only in the damaged biliary vesicle. The fact that none of the 58 gallbladders contained gallstones, however, does not militate against the possibility that in pregnancy the stage is set for the precipitation of cholesterol. Furthermore, while Newman[23] and Andrews and his associates[1] have stressed the importance of the lowered bile salt content, Walsh[35] reached the conclusion that altering the interrelation of the cholesterol fatty substances and bile salts or acids in the gallbladder alters the ability of the bile to hold cholesterol in a watery solution. The sequence of events might therefore be as follows: Stasis resulting at first in an increasing concentration of bile salts, with resultant damage to the gallbladder wall, alters the concentrating power of the mucosa and thereby changes the normal ratio of the constituents of the bile. If metabolic disturbance or infection be then superimposed on stasis, precipitation of stones might well follow. Because of these enumerated findings, Gerdes and Boyden expressed the belief that the stasis of pregnancy sets the stage for the sequence of events which results in the greater incidence of gallstones among women who have borne children. Ivy,[17] in discussing the physiologic factors which play the most prominent role in the production of stasis in the biliary tract, mentioned duodenal irritation or inflammation; reversed peristalsis in the duodenum; spasm of the sphincter of Oddi due to nervous reflex disturbances or inflammation of the ampulla of Vater; motor inactivity of the gallbladder due to the presence of too little fat, fruit juice or meat in the diet; an abnormally small cystic duct, requiring greater activity on the part of the gallbladder, and the possibility that a sphincter may be located at the neck of the gallbladder (problematic).

He expressed the conviction that the chief factor concerned in causing the gallbladder to contract and evacuate is the hormone cholecystokinin, which is elaborated when fats, acid fruit juices, gastric juice and possibly peptones come into contact with the upper part of the intestinal mucosa.

Pain, mild or severe, in the biliary tract is often produced by contraction of the gallbladder and spasm of the sphincter, producing spastic distention of the ducts—this in the absence of gallstones. Such a disturbance in the motor state is termed biliary dyskinesia or dyssynergia.

Gallstones.—Gallstones may be formed in the gallbladder or in the bile passages and may be single or multiple; if the former they are nonfaceted and if the latter they are faceted. They are composed of cholesterol and bile salts, mostly, with degenerated cells of various kinds. There are two types of stone, the metabolic or aseptic and the inflammatory or septic.

The metabolic stone is usually single and white and may become large, being composed almost entirely of cholesterol. It is thought by some observers that cholesterol is held in solution by the action of the bile acids, and that disturbances regarding the proportions of acids and cholesterol, particularly an increase of the latter, may result in a precipitation of the cholesterol. In many instances there is absolutely no clinical evidence of the presence of the stone, even though it may eventually become large; and though the gallbladder may present no evidence of inflammation, yet such a stone may become impacted in the duct or neck of the gallbladder, with resultant stasis which might lead to infection. If infection should be brought about, there might ensue a combination of bilirubin calcium with cholesterol, this combination eventuating in the formation of multiple stones. It should be emphasized that the formation of a pure cholesterol stone is favored by a high cholesterol content of the blood and bile and stasis in the gallbladder.

Pure pigment stones are multiple, very small, black, brittle and hard, and contain no cholesterol. They are often found in cases of hemolytic jaundice. The infective or septic stones are the faceted cholesterol-pigment-calcium stones, presenting a concentric arrangement of laminas. They of course vary greatly in size. This type of stone is formed in a medium rich in protein, while the pure cholesterol stone is formed in a medium poor in protein. With inflammation, resulting in the formation and mixture of pus, mucus, bacteria and epithelial cells, the gallbladder becomes more or less a closed cavity; but as the swelling subsides, bile again enters the gallbladder, and there follows a deposit of layers of cholesterol and bilirubin calcium around the nuclei of organic matter, resulting in the formation of multiple faceted septic stones.

Gallstones may give rise to symptoms in their passage along the cystic and common ducts or during their occupancy of the gallbladder. Because of their ability to wander into the ducts, the small stones are more likely to cause trouble than the larger stones which cannot enter the small ducts; however, the large stones confined to the gallbladder can and do precipitate symptoms. Gallstones of the usual type are associated with inflammation of the gallbladder.

Because of the continued irritation resulting in inflammation, the wall of the gallbladder becomes thickened, causing a marked diminution in its cavity. It may not be amiss to restate Courvoisier's law, which is that in jaundice due to pressure on the common bile duct from without, as from cancer of the head of the pancreas, the gallbladder is distended, whereas in jaundice due to impaction of a stone in the common duct, the gallbladder is usually contracted. A stone may become impacted in the cystic duct, causing the gallbladder to become greatly distended with mucus, yet it is perfectly possible that the distended vesicle may contain stones. One should remember that a stone may be imbedded in a pocket in the gallbladder wall, whence perforation may take place into the peritoneal cavity or the large or small intestine; if into the last, obstruction may occur.

The problem of gallstone formation has not as yet been solved; there are several factors, (1) bacterial infection, (2) stasis of the bile and (3) a high cholesterol content of the blood.

1. **Infection** is undoubtedly the most important factor, causing a precipitation of the various elements necessary to the formation of gallstones; that is, a precipitation of the cholesterol and of the bile pigments, probably owing to interference with the bile salts, on the presence of which depends the solubility of both the cholesterol and the bile pigments.

As is well known, typhoid fever is a common factor in the production of gallbladder infection, and the typhoid bacilli are often found. Lewellys Barker reported that living bacilli were found in gallstones removed thirty-five years after an attack of typhoid fever.

2. **Stasis of the bile** is most likely to bring about a precipitation of the solids, and this may be due to the patient's sedentary mode of life, to obstruction or to muscular atony.

3, **The Cholesterol Content of the Bile.**—Typhoid fever and pregnancy, two conditions associated with calculus formation, produce a great increase in the cholesterol content of the blood and bile. Gallstones are much commoner in the stout woman who has borne children.

Boyd[5] emphasized the fact that cholesterol is held in solution in the bile in a series of loose and firm complexes with the bile salts, and if by some means the bile salts are removed, the cholesterol is precipitated; also, there is no differential absorption of cholesterol and bile salts from the normal gallbladder; the infected gallbladder, however, absorbs the bile salts rapidly, and cholesterol slowly if at all; therefore in cases of cholesterol stones the bile acid content of the bile is always low.

Cholesterol content and infection, the factors most likely to cause gallstone formation, are liable to periodic fluctuations, and the cholesterol content of the blood and bile will rise with each pregnancy, only to fall to normal in the intervals. After each attack there is no doubt that the gallbladder is left more damaged.

Relative to the chemical factors concerned in the formation of gallstones, Dolkart and his associates,[11] after a thorough study, concluded that analysis of human bile showed the concentration of the saponifiable fraction to be extremely low in proportion to that of the nonsaponifiable or cholesterol fraction. These findings indicate that the fatty acids in the bile play a significant role in maintaining cholesterol in solution and in preventing the formation of gallstones; they also show that the action of fatty acids in this connection is much greater than the action of the bile salts or the bile acids. These authors further stated that they do not agree that the mechanism whereby cholesterol is held in solution in the bile is chiefly a function of the bile salts.

SYMPTOMATOLOGY

The history forms one of the most fascinating chapters in the study of gallbladder disease; its preëminent importance cannot be overemphasized, and I lay more stress on a thorough case history, carefully taken and judicially appraised, than on any other single factor in diagnosis.

An acute gallstone attack is most likely to occur in a woman who has borne one or more children; her age may range from thirty to sixty years, but gallbladder disease probably begins in the majority of instances between thirty and forty. The pain is usually in the epigastrium or some portion of the upper part of the abdomen. There is no particular time for it to appear, though in most cases it manifests itself in the early morning hours. The reason advanced for this is that the average person eats the heaviest meal at night, and this meal is likely to contain the largest amount of fat taken during the day. In this regard it is interesting to speculate as to why the patient, in whom subsequent operation proves that the gallbladder contains many stones, went through so many years of life before the acute outbreak occurred on this particular occasion. The pain, whether sharp, shooting or of some other type, may be mildly severe or really agonizing, requiring the use of a large dose of a narcotic; it may remain in the epigastric area or radiate along the right border of the costal margin to the back, to the angle of the right scapula or to the shoulder; on occasions it may go through to the back. I have at odd times observed pain radiating to the left or originating on that side, and it has been suggested that possibly this atypical location is due to pericholecystitis or pancreatic involvement. The onset is usually sudden and the pain constant, although remission is at times noted. No one can predict the length of time that pain will persist; it may spontaneously disappear quickly; or again, after a hypodermic, it will suddenly or gradually disappear, being replaced by soreness and tenderness at the site, which may remain for hours or for several days, depending on the degree of inflammation and spasm incited by the inflammatory reaction; again, all subjective symptoms may disappear with the cessation of the attack; this is inexplicable. Nausea and vomiting may be mild or severe or entirely absent. The temperature is entirely dependent on the degree of inflammation (at times it is preceded by chilly sensations or distinct chills); it usually ranges from 100 to 101 F., though if a severe gangrenous state exists it will rise to 105 F. or higher. The leukocyte count shows a moderate elevation, usually up to 10,000 or 15,000, but it may be considerably higher or lower, the degree of inflammation being the arbiter. The upper part of the abdomen in the region of the gallbladder and contiguous parts is often tender, with muscle spasm; one is frequently able to palpate a distended sensitive gallbladder and an enlarged liver. From the first I always carefully inspect the scleras and all portions of the body for evidence of either mild or marked jaundice, knowing that if the cystic duct only is blocked, jaundice will not appear except accompanied by angiocholitis. If there is blockage of the common duct, however, jaundice in greater or less degree will be observed, with pruritis very often a most annoying symptom. The pulse rate may not be increased, though if fever is present acceleration is noted.

An attack of acute cholecystitis in the absence of stones may cause excruciating pain, a rise in temperature and all the subjective and objective signs I have enumerated except jaundice, which is less likely.

Like all other organs and tissues, the biliary tract may be the seat of inflammatory changes of varying degree; so when there is a mild reaction, the symptoms may be atypical and unusual, masquerading in what physicians are wont to term functional dyspepsia, "ordinary stomach ache" or "biliousness." A patient with such manifestations should be closely observed after the acute attack in order to discover whether the inflammation is subsiding or is progressing to the ducts, or if there is developing a fulminating process which will ultimately manifest itself as an empyema. Observation should include temperature, pulse, respiration and leukocyte count; the mucous membranes and skin should be repeatedly inspected to detect the first evidence of jaundice; the urine should be studied as to color and possible bile content and the stools examined systematically for the acholic, putty-colored type, which indicates a blockage of the common duct. Elevation of the icteric index is indivative of an extension of the inflammatory process, so careful checking of this value is important.

If the following symptoms, signs and findings are observed, one may feel sure that cholangitis is present: low grade fever, anorexia, secondary anemia, constipation, marked malaise, coated tongue, sallow complexion, slightly subicteroid tint of the scleras and possibly a moderately enlarged spleen with a tender, palpable liver. Traces of urobilin, urobilinogen and bile may be discovered in the urine. Usually the gallbladder is not visualized by the Graham test. It is most advisable to make a biliary drainage investigation as to the cytologic and the bacteriologic content. If several studies prove the presence of the streptococcus viridans, one may be positive that advanced infection of the ducts is present. Should the infection spread throughout the liver, septicemia will almost certainly result.

With chills, markedly elevated temperature, up to, say, 101 to 104 degrees, jaundice, high leukocyte count and all the earmarks of a septic state, one can be sure that an acute and severe cholangitis is present, and one becomes apprehensive lest pylephlebitis and acute pancreatitis ensue, as both are life-threatening complications. The bacteria most often involved are streptococci, the bacillus coli and the bacillus typhosus. It has been claimed that parasites are at times the inciting cause, the echinococcus and the ascaris lumbricoides being the most frequent offenders.

Chronic gallbladder disease, from a historical standpoint, is not nearly so simple as the acute phase. There is one outstanding feature, however, on which splendid work has been presented during the past several years, and I am aided greatly by the proved fact that the majority of persons with persistent digestive complaints who harbor structural disease ultimately prove to be afflicted with hepatobiliary abnormality. This is particularly apt to be true of a middle-aged woman who has borne one or more children. One must be always on the alert, therefore, when such a persons consults one because of low grade but persistent gaseous dyspeptic symptoms.

Many patients show absolutely no subjective symptoms or objective signs indicative of biliary tract disease; in fact, except for persistent dyspepsia, the patients appear, and prove later by thorough examination to be, of a particularly rugged type. If the disease is of the metabolic type, the inroads on their physical being may be slight; but if it is of an infective character, the general health may be decidedly impaired. In most patients the discomfort is not referred to the gallbladder region but rather to the epigastrium and upper part of the abdomen. On thorough palpation not the slightest tenderness or muscle spasm may be noted, and from a physical standpoint, the liver is not enlarged or tender, and the gallbladder is not palpable. In other patients there will be marked upper abdominal sensitiveness on palpation. In contradistinction to this type is the often encountered "livery" person, with a sallow complexion, "liver spots" scattered over different parts of the body and sometimes xanthelasma containing deposits of cholesterol, most likely to be located on the upper and lower eyelids, although some authors have called attention to dark circles under the eyes. Because of the low grade infection with a dyspeptic state, which induces many patients to restrict diet and ingest a markedly inadequate food supply, there is a picture of chronic fatigue, malnutrition and lack of sustained endurance—in short, of constitutional inadequacy.

The dyspeptic complaints consist of heartburn, fulness, distress and other sensations which the patients find difficult to describe adequately; these symptoms are mostly in the upper part of the abdomen, often appearing during eating or immediately thereafter. One symptom which should be stressed is the sensation of fulness and distention after ingestion of a few mouthfuls of food; I think this is in all likelihood due to a combination of cardiospasm, pylorospasm and a hypertonic, hyperperistaltic state of the stomach. Pain is unusual with this type of dyspepsia. On many occasions I have been led astray by the patient's saying that distress and discomfort frequently occurred three or four hours after meals and might be temporarily but only party relieved by eructation following a dose of soda. On hearing such a statement, I now immediately proceed to close questioning: Will food or a glass of milk produce worth while and complete relief? Does the patient suffer nocturnal outbreaks of the same type? Do milk and various articles bring about practically complete relief for some hours? Are the attacks almost clocklike in regularity? All things being equal, and with a lack of this clocklike regularity of symptoms, I become suspicious of gallbladder dyspepsia. A large number of persons present what I term "fat indigestion," that is, they are particularly intolerant of fatty articles of diet; and if detailed questioning elicits such a history, it is of great help. Valuable information can be obtained by intimate questioning, each question having a definite objective. I cannot emphasize too strongly the invaluable aid of a meticulous history. These patients often complain of a disagreeable taste on awakening in the morning; this is not surprising when one considers that with dyspeptic symptoms, lack of appetite or sitophobia their intake of solid foods is diminished and the proper stimulation of the salivary glands does not take place; the ensuing over-growth of oral bacteria results in a disagreeable taste and a bad odor to the breath. It is no wonder that most of these patients lose weight, and in consequence have many general complaints, such as various and sundry aches and pains throughout the body and joints, which they report as "rheumatic pains." Like all dyspeptics they become finicky and fussy about their food, and because of discomfort and "gas," proceed, under the advice of well meaning physicians, to diminish food intake until in many instances they are really on a starvation diet. The medical adviser, alas, does not suspect the biliary tract as a source of their nervous dyspepsia. Continued and substantial weight loss is a warning; no matter what the apparent cause, the physician should always be suspicious of a malignant factor in the offing and never let it slip his mind.

With infection, there is lack of appetite, which in turn causes a great diminution in the bulk of food. Abnormal intestinal function practically always ensues, usually in the form of constipation and its accompanying discomfort, there may also be seemingly innumerable sensations, described by most patients in great detail and markedly over-emphasized. While not usual, achylia gastrica may coëxist with biliary disease, and in contradistinction to the constipation there may appear a gastrogenous diarrhea. This possibility should always be borne in mind in a case of biliary disease and diarrhea. The indicated therapy, application of dilute hydrochloric acid, will in many but not all cases bring about a miraculous alleviation of the condition, though, needless to say, not necessarily a diminution in the biliary symptoms.

The physician called in the early morning hours to attend a patient with an undoubted gallbladder attack should not be misled by absolute denial of previous annoyance with dyspeptic symptoms. Strange as it may seem, untoward digestive reactions may never have been noted in many cases. This finding is analogous to that of ruptured peptic ulcer or severe gastric hemorrhage in a patient who on the closest questioning categorically denies ever having had a digestive symptom. There is no adequate explanation of such phenomena.

Often noted in gallbladder disease are symptoms which definitely and absolutely mimic duodenal ulcer; I think in most instances such symptoms are due to a reflex pylorospasm or duodenitis, both of which frequently accompany the disease in question; but it is not extremely rare for duodenal ulcer and gallbladder disease to appear simultaneously. Appetite is in most cases diminished, and this is easily understood; while nausea and vomiting occur, they are not outstanding in the majority of cases and are of course more frequently met in the acute attacks. In the low grade type of biliary infection my experience has been that upper abdominal sensitiveness is not an outstanding feature and is just as likely to be absent as present.

A relation to foci of infection—in the teeth, tonsils, sinuses and so on—as well as to food allergy, undoubtedly exists, and to the question "Does an infection of the biliary tract play a role as a primary focal infection?" there can be only one reply, in the affirmative.

Various infectious diseases, such as typhoid fever, scarlet fever and influenza, are spoken of as being primary factors in the production of biliary tract infection. As I have indicated, the indecisive character of symptoms renders it not unusual for biliary disease to be present and to continue for many years with or without mild or outstanding symptoms. It is imperative to remember this and be always suspicious of its existence when after careful attention to hygienic, dietetic and medicinal measures the various symptoms fail to yield to therapy. Particularly is this important when a flatulent dyspepsia persists in a middle-aged, depressed, possibly neurotic person, more especially a woman who has borne children.

It is important in every case of painless jaundice which is progressive and afebrile always to be alert and suspicious of carcinoma of the head of the pancreas. In this condition a complete blockage of the duct ultimately results; this is in most instances at variance with the action of a stone, the latter rarely producing absolute obstruction. Rehfuss and Nelson,[29] quoting Fiessinger, presented a very illuminating table for differential diagnosis between calculous and cancerous obstruction:

Calculous Obstruction	*Cancerous Obstruction*
1. Usually women have had one or more antecedent attacks of biliary colic	1. Men forty to fifty years of age, often without antecedent colic.
2. Sudden onset following colic.	2. Intense jaundice—becoming greenish or brown.
3. Moderate jaundice, variable in intensity.	3. Large, rounded, pear-shaped gallbladder.
4. Small gallbladder not palpable.	4. No special tender points.
5. Tender points over pancreaticoduodenal angle.	5. Often with acholic stools—deficit in meat and fat digestion.
6. Stools show simple acholia without perceptible alteration of fat or protein digestion.	6. Progressive emaciation.
7. Irregular emaciation.	7. Possible glycosuria.
8. No sugar in urine.	

These authors also called attention to an important clinical picture, namely, a severe jaundice caused by cirrhosis of the liver, which is persistent; the condition is due to involvement of the hepatic cells and not the ducts. Of diagnostic value in such cases are the presence of ascites, collateral circulation, hard liver and splenomegaly.

Attacks of gallbladder disease are often initiated by diabetic indiscretions; however, nervous shock, physical exertion and marked fatigue may inaugurate an outbreak. While weeks, months or years may intervene between attacks, as the disease progresses the attacks become more frequent. In all cases of upper abdominal pain, even though one feels more than reasonably sure that the gallbladder is the offending organ, one must bear in mind the possibility of nephrolithiasis, which often masquerades under the symptom complex of disease of the gallbladder with or without stones.

Infrequent but eminently important, immediately after a successful cholecystectomy in which the preoperative diagnosis was verified, there may occur excruciating pain exactly similar to that complained of during the acute outbreaks preceding the operation, and serious consideration is often given to immediate reoperation. The symptoms may or may not be accompanied by fever, acceleration of the pulse and other concomitant symptoms indicative of infection. Happily, the attacks usually subside and normal convalescence ensues; such episodes I consider due to dyskinesia or a temporary, mild or moderately severe cholangitis. In another type, however, weeks or months may elapse before severe attacks of pain appear, and this type resists the usual modes of therapy. If duodenal drainage is installed, the first bile obtained is thick and viscid, flowing with difficulty; there are single and clumped white cells, mucus plugs and cholesterol crystals; cultures often show *Str. haemolyticus* and *B. coli*; in short, the symptoms have been caused by cholangitis. On the other hand, on occasions a stone is overlooked; again, nephrolithiasis may be an accompanying complication; or an unsuspected and atypical peptic ulcer, duodenitis or colitis may be the underlying factor. It is even possible that some lesion in another organ in the abdomen or elsewhere may be causing the syndrome so vividly portrayed by outstanding symptoms through a reflex mechanism. In this group may be included the complaints of the ever-present psychopath; however, I always consider that the outstanding complaints are justified until I have completely satisfied myself of the absence of structural or definite functional disturbance such as true spasm, which, as is fully known, is capable of causing severe discomfort and pain.

Of vast importance is a discussion of the relation of gallbladder disease to cardiac disease and symptoms. In an excellent article, T. R. Brown[7] called attention to the significant fact that in certain cases coronary thrombosis and angina pectoris have been incorrectly diagnosed as gallstone colic; he also emphasized the point that certain diseases of the liver and biliary tract, notably cholecystitis and cholelithiasis, have definite symptoms referred to the heart, and in some cases there is true organic disease of the heart, in the origin of which it is possible, though not usually probable, that the diseased gallbladder has played a part. In a small number of cases, gallbladder disease has not been diagnosed or even suspected, and the trouble has been treated as purely cardiac in origin. It is an accepted fact that the agonizing pain of gallstone colic may markedly derange cardiac action and may produce palpitation, disrupted rhythm, bradycardia or tachycardia; even death of this origin has been reported. There really appears to be a true relation between organic disease of the heart and of the gallbladder, and it is well known that angina pectoris or coronary thrombosis may similate biliary colic and be treated accordingly; also, the exactly opposite condition may occur, though it is much less common. Brown presented a group of cases in which the symptoms were regarded as entirely cardiac, yet finally the gallbladder was shown to be definitely diseased and its removal produced either complete disappearance or marked amelioration of the cardiac symptoms. He concluded that if there are reasonable data on which to base the diagnosis of definite gallbladder disease, even when the symptoms point largely toward a cardiac origin, it is justifiable to attack the gallbladder in the hope that marked relief may be obtained. If there is considerable doubt, however, it is obviously far wiser and far safer to treat the condition as cardiac.

Starr[31] called attention to the rather frequent occurrence of cholelithiasis, diabetes and arteriosclerosis and expressed the opinion that the mechanism of arteriosclerosis is closely allied to that of gallstone formation; furthermore, coronary thrombosis is one of the results of atherosclerosis, and the frequent coincidence of this lesion in the heart with that in the gallbladder is to be anticipated. After presenting illustrative cases, he gave the following summary:

> 1. As regards differential diagnosis, it is necessary to realize that both conditions are frequently present. The occurrence, in other words, of the positive laboratory findings of one condition does not exclude the possibility that the symptoms studied may actually have been due to the other condition also present. This is particularly true when coronary symptoms are present, since the electrocardiographic findings may develop slowly. . . .
>
> 2. There seems to be no causal relationship between the two conditions although disturbances of cardiac rhythm may well be due to gallbladder dysfunction. . . . This, however, is quite different from producing cardiac infarction. The difference in the occurrence of coronary pathology between the two groups of patients of the same age distribution, who had and had not had gallstones, is not significant.
>
> 3. Patients with advanced coronary disease will withstand cholecystectomy if required by the clinical course of the gallbladder disease.
>
> 4. But this (removal of the gallbladder), as these cases indicate, will not prevent subsequent cardiac pathology. . . .
>
> From the point of view of medical practice we must realize that disordered fat metabolism may have these two serious results and attempt to forestall their development by correcting the biochemical disorder early in life.

DIAGNOSIS

A carefully taken and judiciously studied history constitutes the most important single factor in the diagnosis of gallbladder disease, and as a serious attempt at least has been made to incorporate the most important points in the section allotted to symptoms, it would seem repetitious to present them again here. It would not be amiss, however, to call attention to the vagaries and protean characteristics of this diseased state in its acute, subacute and chronic forms.

Practically every authority working in this field is of the opinion that the greatest step forward in diagnostic procedure was accomplished by Graham and his co-workers when they presented the technic for gallbladder visualization; it has been invaluable, and roentgenologists are growing daily more expert in the technic and the interpretation of roentgenograms.

Some years ago Lyon made practical application of the physiologic principles enunciated by Meltzer; the details of the procedure are familiar to every one, and of its value as a diagnostic and therapeutic agency in many cases there can be no doubt. By this method worth while information may be obtained as to the physical characteristics, chemistry and cytologic and bacteriologic content of the bile; it is most helpful when used in conjunction with *x*-ray studies, though this method has always been handicapped by the fact that the bile used is mixed with, and contaminated by, gastric pancreatic and intestinal secretions. An enormous amount of work along this line has been presented, and many authorities are of the opinion that the dark bile denominated "B" has been proved to originate in most instances in the gallbladder.

There is much difference of opinion among authorities as to the real value of gallbladder drainage; so it may be well to present what seems to be the consensus of those having the most experience. First, they feel that if a considerable specimen of dark "B" bile is obtained, the interpretation must be that the gallbladder is discharging its contents; this is not always true, however, for dilated biliary ducts may harbor a dark bile. Then come the questions "If 'B' bile is not forthcoming, is there a definite obstruction? If so, what is its character?" The answer is that the same factors prevail here as with the nonfilling of the gallbladder observed by the Graham test; after proper therapy a free flow may appear if there is no stone. leading one to believe that spasm or inflammation with temporary edema had been present or that a small stone may have become dislodged, thus allowing proper drainage.

The microscopic observations undoubtedly possess marked diagnostic value separately, but particularly in conjunction with the Graham visualization test. The following abnormal elements have been described by various authors: *Lamblia* (*Giardia*) *intestinalis*; cholesterol crystals, most authorities being of the opinion that these crystals have an outstanding diagnostic value indicative of gallstones; calcium bilirubin pigment, possibly as significant as the cholesterol crystals; bile-stained pus cells; columnar epithelial cells, and lipoid material. These last findings are thought to be indicative of a catarrhal condition of the gallbladder and ducts. If a large amount of saliva is swallowed, squamous cells, pus cells and salivary corpuscles will markedly contaminate the duodenal contents.

In addition, bacteriologic investigations, though contamination is certain in most instances, are important if the same organism continues to predominate in the "B" bile. Various forms of streptococci and staphylococci as well as colon bacillus are encountered, and as the latter is most frequently found, it is thought possibly to be the infecting organism. Chemical investigations of bile acids, cholesterol and cholesterol esters are being carried out, and decisive findings of great diagnostic value will undoubtedly result.

A detailed discussion of the various differential characteristics is impossible here. One or more of the following disease entities may play an outstanding role in the symptom complex (I think it would be helpful always to consider first the other organs of the digestive tract and their potentialities as harborers of disease); peptic ulcer of the stomach and duodenum, carcinoma of the stomach, abnormalities of the duodenum, gastric crises of tabes dorsalis, diseases of the liver, pancreatic involvement, an irritable, inflamed, ulcerated colon, appendicitis, intestinal obstruction, nephrolithiasis, pyelitis, ureteral stricture and cardiovascular disease—coronary thrombosis or angina pectoris.

In a recent article, Levinson[20] stated that duodenal drainage in the early stages of acute catarrhal cholecystitis may show polymorphonuclear leukocytes, various types of cells, bacterial colonies, mucus and the infective organism, such as the staphylococcus, the streptococcus or the bacillus typhosus, which may be isolated by cultural methods. In acute suppurative cholecystitis there is also an elevation of the leukocyte count, to 20,000 or 30,000, with a marked increase in polymorphonuclear leukocytes, and as the disease becomes chronic the leukocyte count approaches the normal level.

Trumper and Cantarow[33] emphasized the value of the icterus index in various conditions, stating that it may be decreased in severe secondary anemia, though increased in hemolytic processes, such as malaria, bacteremia, septicemia, hemolytic jaundice and obstructive jaundice; in hepatic insufficiency (cholangitis, hepatitis, hepatic necrosis and catarrhal jaundice); in pernicious anemia and splenic anemia, and in internal hemorrhage (retained).

TREATMENT

The treatment of gallbladder disease offers a challenge, as many problems are yet unsolved, and the ideas of competent men continue to conflict. Some wish to adopt radical procedures medically and surgically; another group is decidedly conservative in its attitude, and yet another school desires to apply physiologic principles together with a combination of the more successful radical or conservative measures.

In this as in all disputed matters, the medical profession swings violently to either right or left until some sane, judical minds call it back to the middle realm of calm consideration by demonstrating that with the abstract scientific facts must be mixed a goodly amount of common sense.

The yeoman pioneer work of Boyden, Whitaker, Mentzer, Ivy and other sincere and capable investigators has, in recent years, been carried forward by a small army of competent scientists and clinicians—Jordan, Lyon. Bockus, Ravdin, T. R. Brown, F. G. Brown, Dolkart, Mock, Portis, Rehfuss, Mann, Blackford and E. Graham, to mention only a few.

A marked advance in therapy was brought about when workers like Blackford and Dwyer[3] showed by thoroughly studied statistics that persistent abdominal symptoms when dependent on intra-abdominal disease are due in at least 50 per cent of cases to gallbladder disease. A very illuminating postmortem study by Crump[10] led to the arresting statement that 40 per cent of the adult population harbor gallbladder disease. Such striking evidence of the frequency of involvement of this organ proved a great stimulus to the study of diagnosis and therapy.

Some years ago various investigators proved that the ingestion of magnesium sulfate and fats—the latter in the form of cream, butter, olive oil, egg yolk and oleic acid—definitely accelerated the activity and emptying of the gallbladder, being much more efficacious than bile salts empirically used. From the pharmaceutical standpoint, indeed, bile salts were often too unskilfully prepared for effective use.

With the development of comprehensive knowledge concerning the newer aspects of physiology, particularly Ivy's contribution showing the presence and direct action of cholecystokinin, a veritable flood of varying methods of medical treatment was loosed. Physicians, a gullible group, proceeded to accept the various suggestions proposed, apparently adopting those which were most plausibly presented by the essayist and "sounded" best.

The application of magnesium sulfate, in large or small doses, became the vogue; with this usually a low fat, low cholesterol diet was given. Medicinally, the favorite formulas were the "accepted" biliary disinfectants, such as the salicylates and different hexamines, and bile salts in various combinations, *i. e.*, pancreatin, cascara and other laxatives.

There is no gainsaying the fact that restricting the diet and activity and keeping the bowel free with magnesium sulfate and other laxatives did, for a while at least, result in amelioration of symptoms in many cases. But certainly in the majority of cases there was, after a period of varying duration, failure of sustained response; it appeared that the magnesium sulfate would upset the digestive tract, and the symptoms in greater or less degree would return. This occurred often in my own practice.

Aided by comprehensive study of the work of many competent observers, I finally arrived at the definite conclusion that in a majority of cases the symptoms were due to biliary stasis—I mean, of course, when the symptom complex indicated a smoldering larval type of underlying lesion. When acute symptoms—chill, fever, leukocytosis, rapid pulse and all the other signs of a fulminating type of attack—were noted, it was readily realized that there was an active complicating factor in the form of bacterial invasion with acute inflammation; this might at times lead to acute "blocking by edema"; in some instances it indicated that necrosis and pus formation with necrotic changes had occurred.

Now all physicians, I think, are convinced that nonvisualization of the gallbladder is due to one or more factors; there may be some pathologic state of the liver, a disease of the gallbladder wall or an obstruction of one or more of the ducts; with any one or a combination of these, bile stasis results. Would it not seem consistent with scientifically proved evidence and common sense to put forth every effort to overcome this stasis by applying measures designed to reduce inflammation and spasm and induce an active, flushing flow of the bile?

F. G. Brown and R. E. Dolkart presented an illuminating and forward-looking article dealing with the medical management of low grade gallbladder disease. Brown some years ago prescribed frequent feedings of smooth foods, and in addition cream and butter; in some instances eggs were added. He was, however, careful to exclude cooked fats, and he made use of antispasmodics. Because of the satisfactory results observed, he continued his efforts along this line while broadening his experience by handling an increasing number of cases.

Being displeased with the use of magnesium sulfate, Brown and Dolkart began the use of ketocholanic acids after it had been suggested to them by K. K. Jones on the basis of its stimulation of the flow of hepatic bile.

It has been proved beyond doubt by various observers that bile acids do have a distinct choleretic influence.

It has also been stated that the ketocholanic acids, which are the oxidation products of the natural bile acids, possess lower toxicity, and that the use of these acids may increase the flow of bile as much as 100 to 200 per cent.

It is confidently believed by Brown and Dolkart that frequent feeding of a high fat diet, together with the application of ketocholanic acids, will in most instances bring about a direct stimulation of liver bile, and with this an increased activity of the entire biliary apparatus as well as the gallbladder. The fat also acts in a physiologic manner by inaugurating contraction and emptying of the gallbladder, and such action results in flushing and draining of the biliary tract. These observers made use of cholecystography to determine objective improvement, though they realized that even this method has its limitations. The excellent and illuminating article by Lahey and Jordan[19] showed the close relation between an irritable colon and gall bladder function, proving that often a gallbladder will not properly fill in the presence of an irritable spastic colon, but when the state of spasticity has been overcome, satisfactory visualization is observed.

The method of treatment I have been discussing should not be applied in cases of acute cholecystitis or obstruction of the common duct; furthermore, there must be a gradual administration of the high fat diet; my criterion of advancement is the reaction of the patient.

In retrospect it would seem that in cases of low grade biliary disease, worth while results are obtained by the judicious administration of frequent (hourly) feedings of milk and cream, as well as of antispasmodics and ketocholanic acids; by this method the flow of hepatic bile is stimulated and adequate emptying of the gallbladder encouraged; there can be no doubt of the value of antispasmodics.

The vast majority of authorities will agree that in the presence of an acutely inflamed gallbladder and biliary passages, stimulation should not be applied; therefore, it should be the rule to interdict fats, acid fruit juices (unless neutralized) and meats. It is best in these cases to administer starches, sugars and cereal gruels; if persistent vomiting occurs, the parenteral administration of dextrose and fluids is of great assistance, and calcium and vitamins A and D will often prove of value.

In addition to sedatives and antispasmodics which are designed to relax a spastic sphincter and thus aid in reducing reflex gastric disturbances, Ivy recommended small doses (10 to 15 grains) of magnesium oxide, because of its apparent soothing effect on the duodenum and sphincter. He allows local application of heat or cold according to the patient's preference, stating that just why this procedure is of value to the gallbladder is not known; it has been noted, however, that in the case of the colon, heat decreases tone and motility. He urgently advised against the use of bile salts for acute cholecystitis, because they increase the work of the liver; he has observed in dogs showing acute infectious ascending hepatitis that intravenous use of dehydrocholic acid did not increase bile flow. Further, in the presence of advanced hepatitis in dogs, biliary antiseptics such as mercurochrome, acriflavine and salyrgan have proved of no value; they do not come through in the bile. However, in the presence of hepatitis not so far advanced, salyrgan has come through into the bile in antiseptic quantities, and the bile has occasionally been seen to clear after acriflavine therapy. Ivy emphasized the fact that he does not look with favor on the use of such preparations for acute disease.

In discussing chronic cholecystitis without stones, Ivy brought out a point which I believe will be valuable in certain instances: that a gland secretes better when it is "primed," that is, it takes a larger dose of stimulant to start a gland to secrete than it does to keep it going after it has been started; he and his associates therefore expressed the belief that it is not irrational to start treatment of the most difficult lesions with the Lyon technic, *i. e.*, the application of magnesium sulfate through the duodenal tube and frequent feedings, which tend to keep the bile thin and moving. In these cases the value of applied physiology is emphasized. Twiss[34] expressed the opinion that 75 per cent of patients with gallbladder disease show disturbances in acidity, yet its importance in producing symptoms and pathologic change is seldom realized. He has repeatedly found that the correction of hyperacidity entirely relieves colic in patients without stones who might otherwise come to operation. Moreover, in patients with hyperacidity who continue to have colic after cholecystectomy, decided relief is obtained when the hyperacidity is subdued. The opposite condition, achylia gastrica, does occur in association with gallbladder disease, and often in such cases biliary tract infection is verified by the discovery of positive cultures.

A thorough blood chemical study is advised, and, needless to say, a Wassermann test is recommended. Blood counts looking toward the discovery of anemia or a high leukocyte count should be made during acute outbreaks, as well as icterus index estimations in cases of jaundice, in order to obtain an indication of the degree of obstruction and its variability. A blood cholesterol determination may prove helpful in dietetic therapy, as a lowered cholesterol ester level may indicate accompanying liver damage.

In order to deal intelligently and completely with gallbladder disease a thorough and comprehensive knowledge of the physiology of the hepatobiliary system is essential; such knowledge is invaluable as an aid in diagnosis and in applying the proper therapy, particularly when one is called on to choose between the inauguration or continuation of medical treatment and surgical intervention.

An increasing majority of authorities is reaching the conclusion that a conservative and thoughtful attitude should be taken toward chronic gallbladder disease without stones, because it is certain that the surgical morbidity in such cases has been discouragingly high. Therefore, even though cholecystography shows the contour irregular or distorted, the emptying time delayed or the concentration defective, medical measures should be instituted and continued until it has been definitely proved by persistence or aggravation of the symptoms that they will not yield to treatment. It is doubtless this group of symptoms which in the past has shown unsatisfactory results postoperatively.

There continues to be controversy, particularly between the surgeon and the internist, as to the indicated and most effective mode of therapy for patients in whom gallstones are discovered during routine examinations and for patients with known cholelithiasis though the symptoms are extremely mild or only occasional slight colic appears. All things being equal, I believe that during a quiescent period the gallbladder should be removed, because one can never be sure that a severe outbreak will not occur; such an attack, if of the fulminating type, may result in a critical or fatal outcome. Some internists and surgeons are beginning to doubt the wisdom of the "iron-clad rule" of cholecstectomy for every patient operated on for gallbladder disease. The controversy is in an early stage, but Ivy presented the interesting observation that a functioning organ is infrequently found after surgical drainage of the gallbladder; furthermore, a gallbladder that cannot be visualized and which harbors infection should be removed because of functional cholecystectomy has already been performed, the physiologic and anatomic changes which result from the removal of a gallbladder that concentrates having already occurred.

In a timely and excellent essay, S. A. Portis[26] asked the question, after a perusal of the evidence presented, whether operative interference is justified when medical measures may keep patients just as comfortable if not more so, indeed, than radical treatment. He emphasized a fact that is only too true, that end-results in many cases of surgical treatment show that the morbidity associated with this therapeutic approach is far too great. In approaching the answer to this question, particularly in the presence of a nonfilling gallbladder, he suggested that surgical intervention be withheld until opportunity has been given to observe the effect of intensive medical therapy. In connection with this line of reasoning, Portis suggested the possibility that gallbladder dysfunction is dependent on a hypothyroid state, which may bring about a hypomotility of the gallbladder, ultimately resulting in stasis. Further, the removal of foci of infection, such as teeth and tonsils, has resulted in the reëstablishment of physiologic functioning of the biliary system. His theory is that the infection may act as a distant allergic antigen and set up in the gallbladder an allergic response to this stimulation.

Statistics have shown the morbidity after cholecystectomy for uncomplicated, noncalculous cholecystitis to be striking and most discouraging; hence the need of intensive study and a spirit of conservatism in subjecting patients to radical surgical measures.

Howard[16] reported an illuminating study by T. R. Brown of a group of 84 patients all of whom had had surgical exploration of the biliary tract at his advice from two to fifteen years before. Four died in the hospital of operative or postoperative complications, a surgical mortality of 4.7 per cent. At operation, of the 59 with a diagnosis of acute or chronic cholecystitis with gallstones, the diagnosis was completely confirmed for 57. The fifty-eighth patient showed gallbladder inflammation with bile "mud," and the fifty-ninth revealed a gallbladder which seemed normal to the surgeon. Under "medical pressure" the operator removed the gall sac, and the pathologist reported "chronic gallbladder." Cholecystitis alone was diagnosed in 25 cases, and it was found alone in 14 and associated with gallstones in 8 others. The cholecystitis diagnosed was not found in 3 cases. Adhesions or a mindly inflamed appendix seemed to be the only organic basis for symptoms in 2; in a third the gallbladder was normal.

Howard concluded that 28 (44.4 per cent) of the 63 who answered questionnaires had been completely cured by operation; 10 (15.8 per cent) had been relatively cured; 12 (19 per cent) were improved, and 13 (20.6 per cent) were not improved.

Forty-nine patients had had cholecystectomy as the primary biliary tract operation. Twenty-five (51 per cent) of them were unquestionably cured; 6 (12 per cent) were relatively cured; 9 (18 per cent) were "improved," and 9 were not improved.

Among the 9 patients who had had cholecystostomy, 2 seemed to be really cured; 3 were relatively cured; 2 were "improved," and 2 were unimproved. Three had had a cholecystectomy after an earlier cholecystostomy. The second operation had completely cured 1, relatively cured 1 and left 1 unimproved. Howard concluded that cholecystectomy is the operation of choice when surgical intervention is indicated for the treatment of cholecystitis with or without stones.

An excellent piece of experimental work on animals, having to do with the effects of removal of the functioning gallbladder, was carried out by Bergh, Sandblom and Ivy,[2] and their conclusions were:

> 1. Removal of a functioning gall bladder results in physiological and morphological changes in the biliary system. Among these changes are: (*a*) slight hepatitis; (*b*) dilatation of the biliary ducts; (*c*) disturbance of function of the choledochoduodenal sphincter mechanism.
> 2. The hepatitis which develops is so slight as to be probably of little clinical significance. It is not sufficient in degree to be detected by commonly employed liver function tests.
> 3. Incompetence of the sphincter of Oddi may permit transmission of pressure into the common duct from the duodenum. This transmitted pressure must be considered as a possible factor in the production of dilated ducts following cholecystectomy.

Mock, Brown and Dolkart[22] took marked exception to present day methods of medical and surgical therapy of gallbladder disease, and it is my opinion that they presented a most able and convincing criticism.

In the first place, they did not subscribe to the accepted view that every gallbladder showing any evidence of pathologic change should be removed, nor to the view that the use of a low cholesterol, low fat diet in conjunction with catharis should be the invariable rule for gallbladder disease under medical care. They expressed the conviction that cholecystostomy deserves a more prominent place in surgical treatment than it now occupies, and also that persons with low grade right upper quadrant symptoms will receive more worth while help from medical than from surgical therapy.

They expressed the belief that the present conception of the medical management of gallbladder disease with low fat, low cholesterol diets in conjunction with saline purgatives has no sound physiologic basis; it has been their experience, based on a study of 120 patients with chronic gallbladder disease, that the use of hourly feedings of milk and cream to induce contraction and emptying of the gallbladder, of ketocholanic acids to stimulate the flow of hepatic bile and of antispasmodic medicines to diminish the irritability of the gastrointestinal tract effectively relieves symptoms and reduces the incidence of colic in the majority of cases. They stated the opinion that statistical data indicate the persistence of morbidity in patients with gallbladder disease after approximately one-third of all operations on the biliary tract. In a large number of patients, therefore, an adequate program of medical management would be preferable to surgical measures.

They expressed the conviction that the removal of the gallbladder does not necessarily bring relief to patients with gallbladder disease, especially that associated with pancreatitis, unless colic and intermittent obstruction have made up the predominant clinical picture. They stated it as their considered opinion that routine cholecystectomy is an unwarranted procedure and that in many cases surgical drainage would be preferable. Finally, they stated that there should be a definite revision of ideas as to what constitutes adequate medical management and what constitute indications for surgical intervention in cases of chronic gallbladder disease.

Walters[36] pointed out that the etiologic agent principally concerned in the development of acute cholecystitis is in most cases a gallstone impacted in the cystic duct, which not only interferes with emptying the gallbladder, but at times produces, as a result of pressure, sufficient interference with the circulation of the gallbladder itself so that edema, congestion and occasionally gangrene and perforation occur.

Stone and Owings[32] expressed decided views regarding early operation, as follows:

> When the cystic duct is completely blocked and increasing tension develops within the gall bladder, there can be no reasonable hope of a spontaneous recession of the process. . . . The logical outcome is rupture with either a localized abscess or a general peritonitis—in other words an extension of disease beyond the organ of its origin. . . . There may be some diagnosticians more gifted than we who can foretell which cases will subside and which will become critically dangerous after several days. . . . Not only are we unable to make this distinction but we have no regrets about it—we think that by prompt operation there is a notable saving of time, pain, expense and danger as compared with the policy of delay. . . . Not only do we regard the acute gall bladder lesion, whether hydrops, empyema, torsion, gangrene or simple acute cholecystitis, as best treated by prompt operation, but again, contrary to general opinion, we believe that in most cases the operation should be a cholecystectomy.

Smith[30] presented his views in part as follows:

> I have been impressed with the favorable postoperative course of patients subjected to early cholecystectomy and have operated before the fever subsided in a majority of my own cases without feeling that an error of judgment had been made, until rather recently when an obese woman of fifty-two, who had had several attacks, succumbed two days following a partial cholecystectomy, with rapidly rising temperature and failing circulation. . . . Patients with acute cholecystitis should not be operated on immediately upon admission without an urgent indication. The surgeon should be ready to intervene promptly if progress is unfavorable. Younger patients in good condition after a day or two of preparation may be operated upon without waiting for the attack to subside. In poorer risks, if the course under observation is satisfactory, it is wiser to allow the acute attack to cool off.

It is most illuminating to review the opinions of Judd and Phillips:[1]

> We shall probably not be able to settle the question of when to operate in the acute cases, but the present tendency is to carry out surgical treatment early in cases of acute cholecystic disease. Apparently there is not the same fear of operating in these cases as there formerly was. We are inclined to think that this is due to recognition of the fact that infection is not always the cause of the condition and

> that these patients can have the necessary surgical treatment with comparative safety. . . . Our study of this group of 508 surgical patients (operated upon at Mayo Clinic) would seem to bear out these conclusions, although the operations were performed by several surgeons, among whom there were bound to be differences of opinion. . . . Although we wish to subscribe to the plan of early operation in acute cholecystic disease, and although this coincides with the opinion expressed in the more recent literature on the subject, nevertheless we feel that there are certain instances when surgical treatment should be postponed. In some cases it should be delayed for a long time. In caring for these patients it will be necessary to consider each one as presenting an individual problem. There is no set plan that will fit all cases. . . . Cholecystectomy will not be permissible in every case, but this procedure should be carried out whenever feasible. . . . No one would feel that a deeply situated, inaccessible, acutely inflamed gall bladder should be removed from an extremely sick person. Cholecystostomy may be all that is warranted.

Walters[36] stated that his experience in the management of the disease led him to believe that if the patient is seen in the early stages of the attack, operation can be carried out with safety. On the other hand, if the patient is not seen until the second or third day of the attack, and the infection should appear to be subsiding, he has found it advantageous in some cases to delay operation for one or more days. Although some generalizations may be made regarding the time for surgical attack, there is no doubt that the manifestations vary so much that decision in each case must be made on its merits, with particular reference to the condition of the patient and the progress of the infection. Finally he called attention to a group of patients for whom cholecystostomy is indicated, namely, those who are obese or elderly and in poor condition. Exposure of the gallbladder and common bile duct of such patients is difficult because of either the extent of the inflammation or the inaccessibility of the hepaticoduodenal ligament.

Cave[9] concluded that the majority of surgeons are obtaining better results by waiting from one to five days before operating on patients suffering from acute cholecystitis. This is thus given for the acute inflammatory process to subside, and the patient is offered the opportunity to be properly prepared for the shock of a major surgical procedure. Further, the mortality rate will be higher in the hands of the majority of surgeons if "immediate" operation is advised in all cases, and finally, more frequent and painstaking postmortem examinations would no doubt throw light on the cause of "liver shock and deaths."

Eliason and North[12] expressed the opinion that early surgical measures in the acute attack as well as in the course of the disease will reduce mortality and morbidity. Judicious choice of the procedure to be employed is necessary. The surgeon should recognize his own as well as his patient's limitations. It may be better to leave a difficult impacted stone behind the duodenum until drainage through a cholecystostomy relieves the dangerous jaundice.

I believe the greater number of surgeons entertain the views presented in the preceding paragraphs. There can be no doubt that early operation for acute cholecystitis is rapidly becoming the procedure of choice.

In biliary colic the pain is often agonizing and calls for prompt and efficacious remedies to subdue the pangs. This pain is due to physiologic change, by which are brought about a rise in gallbladder and intraductal pressure and lack of sphincteric relaxation. It would seem that in most instances the nausea and vomiting are due to reflex pylorospasm. The autonomic nervous system is always actively involved through the vagus and sympathetic nerves, which carry afferent pain stimuli as well as motor fibers to the gallbladder ducts and sphincter.

In most instances biliary colic is due to calculi, and in most instances there is marked stasis and infection.

Fats, in the form of butter, cream and eggs, also protein, stimulate the biliary tract to marked activity in that they bring about a production of the hormone cholecystokinin, under the stimulating effect of which the gallbladder becomes active, the ducts contract and severe pain results. It is therefore best to withhold food by mouth during an active outbreak, and when a subsidence occurs the first food administered should be bland carbohydrates.

The vagus nerve is the motor nerve to the biliary tract. The physician's foremost desire should therefore be to overcome its activity; this is accomplished by the application of proper drugs, the most efficacious of which will be described later. These have been extremely satisfactory in doing away with dry mouth, parched tongue, dilated pupils, blurred vision, dizziness and flushed cheeks, which in so many cases are likely to be brought about by continued effective dosage of atropine or belladonna.

In recent years calcium has been extensively and very successfully used intravenously. The claim is made that it is a powerful relaxant of smooth muscle and raises the threshold for pain sensibility.

It should be remembered that stimulation of the vagus nerve causes contraction and hypertonicity of the various parts of the biliary tract, while activity of the sympathetic nerve brings about inhibitory action. A reciprocal action between the gallbladder ducts and the sphincter of Oddi undoubtedly exists; thus, when the gallbladder contracts, the sphincter relaxes, and *vice versa.*

There is an intimate relation between the activity of the bilary tract and the pyloric and duodenal areas, wherein stimuli arising in the biliary tract will be reflexly manifested by pyloric and duodenal spasm. This pathologic mechanism certainly plays a prominent role in the production of symptoms when the biliary tract is primarily involved; by it also nausea and vomiting are brought about.

The main task in treating this condition is to restore at the earliest moment a physiologic state, whereby the spasmodic contractions and distention which are usually accompanied by stasis may be overcome. It is common for stasis to be coëxistent with infection, which may lower the threshold to pain stimuli, and such a combination complicates and makes more difficult the solution of the problem; in fact, it frequently necessitates prompt recourse to surgical intervention.

However, there is no gainsaying the fact that a number of patients respond satisfactorily to symptomatic and palliative therapy.

Along with the antispasmodics and other remedies one must never fail to remember the soothing effect of local heat, applied dry with an electric pad or a hot water bottle or wet as large, hot, moist fomentations to the site of pain and to the gallbladder area. I am sure that these agents often prove most helpful and effective.

Of late the nitrites have been used frequently in an endeavor to overcome spasm. They are used as amyl nitrite in the form of an inhalant or as nitroglycerin, which may easily be applied sublingually. Their action is usually prompt, but on occasion repeated use is necessary. It is well to remember that the reaction in cases of biliary tract disease may be the same as that in cases of hypertension, namely, dizziness, hypotension and sometimes toxic effects or dangerous collapse. Amyl nitrite perles for inhalation, hypodermic tablets of nitroglycerin ($\frac{1}{100}$ grain) or erythrol tetranitrate ($\frac{1}{4}$ to $\frac{1}{2}$ grain) may be used.

Should such mild antispasmodic treatment and dietary measures fail, then recourse must be made to more potent drugs of the narcotic group, such as codeine sulfate or morphine given hypodermically. As it has been definitely shown that morphia at times causes a spasm of the sphincter of Oddi with resulting increased intraductal pressure, small, inadequate doses may aggravate the pain, and a sufficient amount must therefore be given to overcome the original pain plus that producing the added complication. One-fourth grain of morphine sulfate (to which $\frac{1}{120}$ to $\frac{1}{100}$ grain of atropine sulfate is added) should be given as the initial dose, if necessary this may be repeated. Owing to pylorospasm, narcotics given by mouth may remain in the stomach and later the full dose be delivered to the intestine, to produce toxic effects because of the cumulative action; hence the superiority of hypodermic medication. An alternative is to give the hypodermic tablet sublingually if it is impossible to apply it by syringe.

For the small but definite group of persons displaying an idiosyncrasy toward morphia the physician possesses efficient allies in dilaudid (in doses ranging from $\frac{1}{32}$ to $\frac{1}{20}$ grain) and pantopon ($\frac{1}{6}$ to $\frac{1}{3}$ grain dose, preferably the latter); both drugs should be used hypodermically. More recently perparine, a synthetic narcotic resembling papaverine but much less toxic, has been advocated in intramuscular injections of 0.04 Gm. per hour for two doses. This drug may be obtained in ampoules for intravenous use. Another efficient drug in this category is papaverine hydrochloride, a water-soluble salt of the opium alkaloid which may be administered orally or subcutaneously. The single dose is $\frac{1}{2}$ to $1\frac{1}{3}$ grains; this may be repeated several times.

Suppositories containing codeine, belladonna and various barbiturates are at times efficacious, as is calcium gluconate used intravenously. Because of unforeseen situations and idiosyncrasies, it is often comforting to be conversant with a variety of efficient remedial agents.

The bowel condition would best be managed by bland enemas, preferably of physiologic solution of sodium chloride, as in many cases nausea and vomiting are outstanding symptoms. The frequent unpleasant postoperative biliary colic may be due to various factors, among them the unfortunate presence of an overlooked stone, but in the vast majority of cases it is due to spasm or infection with edema of the duct. Consequently, colic immediately following surgical therapy or at a later date does not warrant panic or undue pessimism; the symptoms and condition should be treated as I have indicated for both stone colic and dyskinesia. Needless to say, if the symptoms are caused by stone, operative interference will unfortunately again be necessary. In colic cases I am a great believer in the use of local heat and urgently advise that an electric pad or various types of hot fomentations be applied to the seat of pain; I am sure this is a most useful adjuvant.

During these acute outbreaks food and drink could best be withheld, particularly if active nausea and vomiting are present. Yet, since it is of vital and fundamental importance that the patient receive adequate fluid, it is best to administer dextrose and saline intravenously; another suggestion is that the patient responds immeasurably more satisfactorily if immediately hospitalized.

After a subsidence of the gastrointestinal upset—and each patient is to be individualized in this regard—I prescribe careful adherence to a bland, liquid, soft purée type of diet; gradual increase in the food intake is carried out as improvement is manifested.

The preoperative and postoperative care of the gallbladder patient cannot be over-emphasized. Ravdin[28] stressed the fact that in few surgical conditions is the preoperative preparation of greater importance to the final outcome, for with the greater number of these perversion of function has occurred not only in the gallbladder but in the liver.

Many liver function tests no doubt are of great value, but as yet none has proved dependable in most instances. They are of particularly small value when mild but distinct derangement is present. One great handicap of most tests is the tremendous reserve power of the liver; as a matter of fact, in an organ whose functional activities are so diversified it is highly probable that no one test could indicate the divergence from normal function of all these activities; furthermore, even though all functions preoperatively are normal, injury to the liver cells as the result of operative trauma and anesthesia may be so great as to convert a normally functioning organ into a completely incompetent one. The surgeon must not, therefore, lay too great a reliance on the results of these tests, for these at times give him a false sense of security. For the determination of bile pigment retention in the blood it would seem that the van den Bergh test is satisfactory.

It is of utmost importance that the patient be carefully examined for the possible presence of cardiovascular disease, renal dysfunction or diabetes mellitus. When cardiovascular and biliary disease coëxist, relief of the latter state acts as a great boon to the patient's health. If cardiac symptoms are marked and proper medication is given for a sufficient time, a surprising number of patients will withstand operation and enjoy great relief from the troublesome condition and symptoms. Ravdin[28] made the arresting statement that in his opinion there is no evidence that the preoperative administration of digitalis to patients suspected of having myocardial disease without total arrhythmia is of the slightest value, and that evidence exists that its use may actually be harmful.

Diabetes mellitus is often encountered as a complication of biliary tract disease and must be carefully treated before operation is considered.

One often observes in cases of obstructive jaundice a serious impairment of kidney function; as with cardiovascular disease and diabetes mellitus, the internist must exert every effort to bring about an amelioration of the condition before operation.

The possibility of hemorrhage in the postoperative stage requires much thought and preoperative preparation, and Ravdin said that he saw no value in the administration of calcium chloride to the jaundiced patient and had not applied this remedy for many years. He expressed the belief that no method will designate with certainty which patients will bleed, and that determination of the bleeding and the coagulation time, as well as of the serum calcium level and the sedimentation rate, are without value.

It would seem that the greater the liver damage, the greater the tendency to hemorrhage; hence the frequency of the latter manifestation in cases of obstructive jaundice, especially with malignant change, and its rarer occurrence in cases of hemolytic or catarrhal jaundice.

Two procedures undoubtedly aid in controlling or decreasing the likelihood of postoperative hemorrhage in the presence of jaundice: intravenous administration of dextrose and blood transfusion as a routine both before and after operation. Just how these measures act is not as yet clearly understood. During the early postoperative phase a continuous venoclysis of dextrose solution should be given.

Ravdin gives all jaundiced patients blood before operation; those mildly jaundiced receive one or two transfusions; those deeply jaundiced or with jaundice of a long duration receive three to five transfusions prior to operation, usually from 250 to 300 cubic centimeters of citrated blood every forty-eight hours. After operation blood is given once or twice but not continued unless bleeding appears; then as many transfusions as seem necessary are given. Hemorrhage may be frequent, but the mortality rate is greatly diminished.

As the liver glycogen is decreased the liver fats are likely to increase, and because the liver fats are likely to condition the occurrence of liver degeneration and necrosis after anesthesia, one can readily realize the value of free intravenous use of dextrose solutions with and without saline, both before and after operation, of the application of a diet high in carbohydrates preoperatively and of the addition of protein, which aids in decreasing liver fat. Furthermore, because there has been observed in some cases of biliary tract disease a hypoproteinemia with delayed wound healing, there would appear to be in these cases an indication for preoperative blood transfusion. With the methods now used, it seems that "pancreatic asthenia" and liver shock occur less often. Even though postoperative hemorrhage does occur as a rather common complication in cases of jaundice, there has been a worth while reduction in the degree of bleeding and in the mortality rate.

Recently Butt, Snell and Osterberg[8] reported the following results of the use of vitamin K in prevention and control of the hemorrhagic diathesis in cases of jaundice: Vitamin K and bile salts were given before and after operation to 28 patients with jaundice; only 3 (11 per cent) of these bled after operation. To one of these the vitamin concentrate was given intramuscularly before operation; in the other two the bleeding was minimal. Vitamin K concentrate and bile salts were given only before operation to 22 patients, and but 1 (4 per cent) bled. None of these patients showed an elevated prothrombin time before surgical intervention. Fourteen patients were given vitamin K concentrate and bile salts after operation only, and 9 (64 per cent) of these bled postoperatively. Inadequate quantities were given to 2 patients, and hemorrhage was found at autopsy. Most of the 9 who bled postoperatively showed the prothrombin time greatly elevated before operation.

It should be the physician's aim so to apply preoperative measures as to bring about a more normal function of liver, heart, kidneys and pancreas.

Walters[36] has pointed out that the optimum time for operation is when the level of bile pigment retention in the blood is more or less stationary, and if the blood bilirubin is increasing or decreasing it is advisable to wait until a plateau has been reached before operation.

A decision in regard to the anesthetic is of great importance, as it has been proved that chloroform, avertin and divinyl are contraindicated (and even ether may prove deleterious) in the presence of anoxemia due to the slowing of the vascular stream in ductal obstruction, which in turn may bring about local anoxemia of the liver tissue. Also nitrous oxide and oxygen do not provide sufficient relaxation. After a very wide experience, Ravdin makes use of spinal anesthesia in the majority of his cases.

When ample time is available to make ready for operative therapy—in short, when the patient is ambulatory and his symptoms have not satisfactorily yielded to treatment—the suggestions of Sidney Portis,[25] made after a comprehensive study of a large number of cases, for the preoperative and postoperative care are helpful. As he suggested, the only wise and proper approach is to hospitalize the patient for at least three or four days before operation, in order to afford opportunity for a complete "check-up" in every particular, including typing for possible blood transfusion.

The diet should receive the utmost consideration, and because of its importance I present an outline suggested by Portis:

Breakfast:	Melba toast with jelly, no butter. Fresh or stewed fruit. Cooked cereal with skimmed milk; one egg. Tea, chocolate or cocoa.
10 A.M.	Strained orange juice plus dextrose, or malted milk made with skimmed milk, plus dextrose or lactose.
Dinner:	Large serving of potatoes or steamed rice or noodles. Two servings of vegetables. Salad with lemon, no dressing. Fresh or stewed fruit or simple cereal, pudding or custard. Melba toast with jelly, no butter. Tea with sugar, if desired.
3 P.M.	Strained tomato juice or eggnog made with skimmed milk, plus dextrose or lactose.
Supper:	Baked potato or cereal with skimmed milk. Two servings of vegetables. Salad with lemon, no dressing. Stewed or fresh fruit. Melba toast with jelly, no butter. Tea with sugar, if desired.
8 P.M.	Skimmed milk with crackers.

Postoperatively Portis starts patients on inhalations of carbon dioxide for one-half to one minute every half hour for six hours; after this the intervals are gradually lengthened until the procedure is finally discontinued at the end of twenty-four hours. Subcutaneous dextrose and saline or dextrose in distilled water are started, approximately 3,000 cubic centimeters being administered during the first twenty-four hours; if myocardial involvement is present, however, smaller amounts are given.

After twenty-four hours, small amounts of fluid (excluding milk and cream) are given; then soft foods until about the sixth day, when recourse may be had to the preoperative diet. No hard and fast rules are laid down as to the amounts and the interval feeding time. The physician should be possessed of both scientific knowledge and common sense and should individualize the treatment; one of the outstanding sins of the profession is what I term "mass therapy."

The icterus index should be noted daily for possession of full knowledge regarding liver function. As to the time for the patient to sit up and other important matters, the usual routine of postoperative care is follows. A careful general diet is prescribed, allowing fats—that is, ice cream, butter and eggs—in moderation; results should be closely observed. Fatty, fried and greasy foods must of course be prohibited.

Should the bowel be in need of aid, simple, mild stimulants such as the plain oils or various combinations of like agents and perhaps an occasional enema of physiologic solution of sodium chloride may be administered; drastic cathartics should be interdicted.

Briefly but comprehensively, Eliason and North[12] gave excellent advice as to postoperative care of patients with biliary tract disease, stating that measures should be directed toward the prevention of hypoventilation and pulmonary complications by attention to posture, deep breathing exercises, change of position, suction drainage of the stomach as a defense against abdominal distention, the prevention of concealed hemorrhage and biliary peritonitis by the use of a drain, the maintenance of liver function by the use of decompression drainage and the administration of blood or dextrose and salt intravenously to sustain metabolic and fluid balance. They expressed the opinion that only by strict attention to these matters can one hope to reduce the mortality and morbidity.

A brief summary of the outstanding methods in treatment should prove of value:

Hygiene.—This will depend on the stage of the disease and the type of reaction produced. If the process is inactive and calls for medical treatment, a usual mode of life is allowed, in which undue fatigue, violent exercise and heavy work are avoided. If golf, tennis, bowling and such sports are allowed, the patient should be warned to desist if untoward reactions are noted. Should there be pain of moderate degree, rest and relaxation will be the order, and if fever with mild leukocytosis is present, bed rest with close attention to temperature, pulse rate, leukocyte count, stools and icterus index is indicated. It should be an iron-clad rule to make a most thorough investigation for possible foci of infection in any and every organ, tissue and system of the body, and if such foci are discovered, removal at the earliest possible moment is advisable. The teeth, tonsils and various sinuses should receive closest scrutiny.

The diet is of great importance, and here again the stage of the disease and the reactions produced thereby must receive immediate attention.

For quiescent cholecystitis it is my practice to allow a general diet, eliminating the fried, greasy foods prepared with synthetic fats, for such articles of food almost always precipitate untoward symptoms. However, I do not interdict fats in the form of milk, cream and butter or eggs in various forms, and I see to it that the patient receives an ample supply of lean meats, chicken, fish, green vegetables and fruit juices. Close attention is paid to the patient's symptoms and the diet changed whenever it seems necessary. The patient should always have explained to him the great advantage of smaller, more frequent feedings, because of consequent stimulation of gallbladder activity and the tendency to relief of stasis, the condition which in many instances causes most difficulty. Should he find it possible to remain at home or to enter the hospital, hourly feedings of milk and cream will often prove most helpful.

If the symptoms indicate an active inflammatory state, bed rest is ordered, with either starvation—depending on the severity of symptoms—and intravenous administration of dextrose or the feeding of bland fluids and the various gruels, tea, fruit juice, gelatin and melba toast. As the symptoms subside, a gradual addition of bland foods is in order. Under careful surveillance, milk, cream, butter and eggs are added. A physiologically balanced diet as to vitamins and calories should be the goal.

Drugs.—Drug therapy for this condition has, in my opinion, proved of great value, and I place great confidence in the efficacy of choleretics to stimulate the secretory activity of the liver, thus aiding the gallbladder and ducts in their functions.

The ketocholanic acids are of undoubted merit and may be obtained in tablet form, the dose being 3¾ grains three times daily after meals. I have mostly used the dehydrocholic or the triketocholanic acid, the latter being a chemically pure bile acid, an oxidation product of cholic acid, which is the basis of all bile acids derived from human or animal bile. It is available in 3¾ grain tablets and in a 5 or a 20 per cent solution of its sodium salt, intended for intravenous administration when rapid and more intense choleresis is required. One outstanding characteristic of this drug is its low toxicity. The claim has been made, based apparently on creditable work, that it increases the production of bile by the liver cells 100 to 200 per cent, in contradistinction to the specific cholagogs, which exert their main action over the gallbladder. The usual dose is one or two tablets three times daily after meals for several weeks, after which it may be preferable to allow a lapse of one or two weeks. The only contraindication for this drug is complete obstruction of the hepatic or the common duct, by either a stone or a carcinoma or other tumor mass.

Bile in the form of purified ox bile and the bile salts are highly lauded by some authorities for their effectiveness as cholagogs; one may use the pure ox bile in a dose of 1 or 2 grains three times daily or the same dose of sodium glycocholate or sodium taurocholate. Between bile salts and the pure bile acid I prefer the latter, because I believe it is not only more effective but less likely to disturb the stomach.

With choleretic treatment, various authorities make use of the salines, such as magnesium sulfate, sodium sulfate and sodium phosphate. These are usually administered early in the morning. At times I prescribe a saturated solution of magnesium sulfate and advise the patient to take from one to four teaspoonfuls in 4 ounces of hot water early every morning in an endeavor to provide a free but not diarrheal evacuation; the same proportions may be used for other salines. It is urgently advised that only mild cathartics be administered and the results closely observed, for if in these conditions an irritable or inflamed state of the colon is initiated its action will be most deleterious to the liver and biliary tract.

Gallbladder drainage by the Lyon method is extensively used by many authorities when gallbladder drainage and activity of the biliary system are desired.

Antispasmodics undoubtedly play a most effective role. Everyone is familiar with belladonna in its various forms, the tincture given in ascending doses until the point of toleration is reached, and with atropine sulfate, given in amounts ranging from $\frac{1}{200}$ to $\frac{1}{100}$ grain two or three times daily, depending on the reaction—that is, dryness of the mouth, flushed cheeks and dilated pupils indicate that the point of toleration has been reached.

During the past few years I have been using other antispasmodics which in my estimation are far superior to belladonna and atropine, being far less toxic and definitely more powerful in antispasmodic action.

The first in syntropan, made in tablet form (50 mg.), for use three or four times daily. For parenteral administration there are ampoules (1 cc. equals 10 mg.), to be given three times a day or as required. Trasentin is made in tablet form (75 mg.), one to two tablets to be given two or three times daily; or an ampoule (1.5 cc. contains 75 mg.) may be given three or four times daily or every two hours for several doses if the occasion would seem to demand it. Novatropine (tablet, $\frac{1}{24}$ grain) should be used in doses of one to two tablets two or three times daily. Bellafoline (tablet, $\frac{1}{250}$ grain) is used in doses of one to two tablets two or three times daily, in liquid form (1:2,000) ten drops three times daily or in ampoules of 1 cubic centimeter (each equals $\frac{1}{125}$ grain of bellafoline). With these antispasmodics I usually combine the hypnotics, the one preferred being phenobarbital; such a combination proves most efficacious as a rule. For sleeplessness I use the barbiturate which seems best suited to the patient.

Lastly, to overcome excessive acidity, the adsorbents containing aluminum hydroxide and kaolin in a gel form are most effectual. I have definite confidence also in calcium carbonate, magnesium oxide and sodium bicarbonate, used either singly or in combination; the combination is, in my opinion, more effective.

CARCINOMA OF THE GALLBLADDER

Carcinoma of the gallbladder and ducts is by no means so rare as some authorities would have one believe. It is usually associated with gallstones, no doubt one reason why a greater number of women than men are afflicted, the proportion being about four or five to one. It has been asserted that primary carcinoma of the ducts is more likely to occur in men.

While the growth may attack any part of the gallbladder, it is most likely to affect the fundus and the commencement of the cystic duct. The type of growth is usually adenocarcinoma, although a papillomatous form has been described. As a rule, the tumor invades the liver at an early stage, and extreme and persistent jaundice is an outstanding feature. Metastases occur rather rapidly, extending at times to the glands along the common bile duct, and cases have been reported of secondary nodules in the umbilicus.

The symptoms are the same as those produced by cholecystitis and cholelithiasis. A tumor mass may be palpated in the right upper quadrant of the abdomen; it is hard and tender and shows progressive growth, together with an increasing jaundice which resists treatment. The patient loses strength and weight rapidly, becomes anemic and loses appetite; in short, at a rather early stage he shows marked constitutional deficiency and impairment of general health and strength. The course is rapidly downward.

The condition is fatal, and the only possibility of rendering aid is by surgical interference early, when it may be possible to extirpate the growth; this is seldom possible, because early diagnosis is extremely rare.

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CHAPTER XX

DISEASES OF THE PANCREAS

INTRODUCTION

The close anatomic relation of the pancreatic duct and the head of the gland to the common bile duct explains the frequent involvement of the latter in diseases of the pancreas; for example, obstructive jaundice may result from inflammatory or malignant disease of the pancreas. On the other hand, pancreatitis is frequently associated with extrahepatic biliary disease. Probably infection originating in the diseased biliary system spreads to the pancreas by way of its ducts or through its lymphatic system, which receives lymph from the gastrohepatic omentum, the gallbladder and the common bile duct. Ulcers of the stomach or duodenum may penetrate into the pancreas, causing acute or chronic inflammatory changes within the latter.

Pain, when present, is usually in the epigastric or left hypochrondriac region. At times it is intermittent, at other times persistent or paroxysmal, as with pancreatic lithiasis. It varies a great deal in severity and in cases of acute hemorrhagic pancreatitis may be associated with circulatory collapse. The pain commonly radiates to the left shoulder or back. Not infrequently the back pain at the level of the upper dorsal or lower thoracic vertebrae is mistaken for that caused by arthritis of the spine. Deep epigastric tenderness is often present in disease of the pancreas; however, it is not pathognomonic of it. Dyspeptic symptoms are common with the various diseases of the pancreas. With advanced disease of the pancreas there may be frequent bulky stools, which will be described later. As a rule the stools do not show the blood, pus or excessive mucus frequently seen with intestinal disease. Loss of weight, emaciation and dehydration are often seen with pancreatic diseases, owing in part to poor utilization and absorption of foods and in part to loss of fluids as a result of the frequent, bulky stools. Occasionally osteomalacia occurs during the course of chronic pancreatic disease.

Glycosuria, seen in cases of cholecystitis and cholelithiasis[14] and of peptic ulcer,[13] is rarely a symptom of chronic pancreatitis. Diabetes mellitus as a result of insulin deficiency in disturbances of the islands of Langerhans will not be discussed here. Neither is spontaneous hypoglycemia or hyperinsulinism within the scope of this chapter. In this connection one must mention also hemochromatosis with the characteristic hemosiderin deposits within the pancreas.

PATHOLOGIC PHYSIOLOGY

The alveolar glands of the pancreas produce essential external secretions, which play a most important role in the digestion of foodstuffs and consist of proteolytic, amylolytic and lipolytic enzymes and of sodium bicarbonate. Probably all the external secretory activities represent independent functions.[16] The sodium bicarbonate neutralizes the hydrochloric acid which enters the duodenum in the gastric chyme. Such neutralization is necessary because the digestive enzymes of the pancreas act best in alkaline mediums. It also prevents injury to the intestinal mucosa. The sodium ion enters into other phases of intestinal digestion, for example, its chemical union with fatty acids to form soaps. Although decrease in bicarbonate secretion has been demonstrated in the presence of pancreatic disease,[10] no clinical significance has been established for it. The pancreas secretes the proteolytic enzyme as the zymogen trypsinogen. After reaching the duodenum the latter is converted into the enzyme trypsin by enterokinase, an enzyme secreted by the intestinal mucosa. The proteolytic enzyme digests all forms of protein foodstuffs, breaking them down into their component aminoacids. The amylolytic enzyme, diastase, converts polysaccharides into monosaccharides; *i. e.*, starch is split into dextrose, and cane sugar into dextrose and maltose. The lipolytic enzyme, lipase, converts fats into fatty acids and glycerin.

Hypersecretion of pancreatis enzymes has been recognized only experimentally.[12a] On the other hand, hyposecretion occurs with various pathologic conditions.[16a]. Great diminution in enzyme secretion leads to the stools characteristic of advanced disease of the pancreas. These stools are bulky and contain gross amounts of fat (steatorrhea), meat and the starch of the ingested food. The presence there of undigested meat with microscopically well preserved muscle fibers is known as creatorrhea and is pathognomonic of exclusion of pancreatic juice from the intestines. The Schmidt nucleus test also is diagnostic of this condition. Numerous other procedures designed to determine various degrees of hyposecretion of pancreatic enzymes have been proposed. Their description, correlation and evaluation are not within the province of this chapter, but are readily obtained elsewhere.[27] Of them blood enzyme determination and quantitation of enzymes in the pancreatic juice are of practical diagnostic value. One of these is the demonstration of an increase in the activity of a blood lipase which occurs with acute pancreatitis[5] and cancer of the pancreas.[8] When detected, the evanescent rise in blood amylase is of diagnostic significance[16c] in acute pancreatitis. The diastase test of the urine is of less clinical value. The other type of examination relates to the quantitation, estimated by their activities, of enzymes secreted in pancreatic juice collected from the duodenum. However, such estimations are valueless unless carried out by suitable technical procedures. A most important factor in the latter is the use of a stimulant which will uniformly produce a flow of pancreatic juice. Chiray and his associates,[6] Farrell and Ivy[11] and Swedish investigators[1] have used secretin. After secretin or mecholyl stimulation, relatively pure pancreatic juice can be obtained through a double-barrel duodenal tube. No admixture of bile is present under physiologic conditions. With these substances as stimuli, enzymatic activities in the duodenal contents can be quantitated and will afford an index of external pancreatic secretory function. This is of diagnostic significance. McClure[16a] has established that food fats will cause stimulation when the pancreas retains the ability to secrete enzymes and that its degree, reflected in the quantitative secretion of these enzymes, is modified by pathologic conditions involving the pancreas. These observations have permitted the establishment of a system of duodenal analysis which allows disturbances in the secretion of pancreatic enzymes and of bile to be determined with relative ease. Using this system, he showed that the effects of pancreatic disease on enzyme concentrations of the pancreatic fraction of duodenal contents may be summarized as follows:

Abnormally low enzyme concentrations occur in the presence of (*a*) destructive lesions involving the head of the pancreas, (*b*) chronic pancreatitis and (*c*) occlusion of the pancreatic duct. Dissociation of enzyme concentrations occurs during convalescence from acute pancreatitis, in the presence of partial occlusion of the duct, cholecystitis and cholelithiasis, after cholecystectomy, cirrhosis of the liver and catarrhal jaundice and much less often with peptic ulcer. These are conditions with which sclerotic changes in the pancreas are commonly present. It may be remarked that disturbances in the digestive functions of the pancreas do not occur as the result of achylia gastrica *per se*.[16a,b]

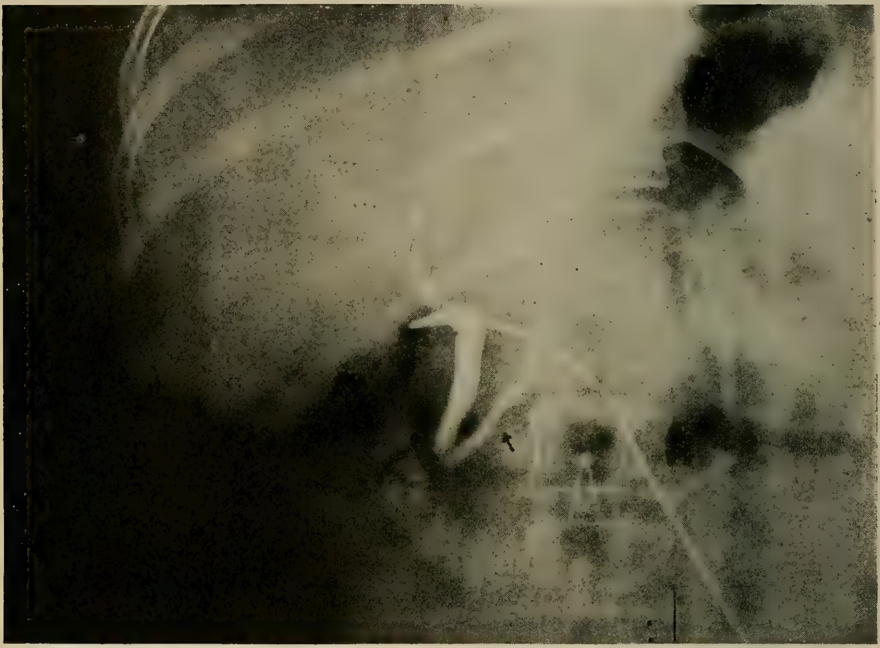

Fig. 93.—Cholangiographic demonstration of the biliary tree and pancreatic (*arrow*) in the presence of proved chronic pancreatitis.

The combined study of the pancreatic and biliary fractions of duodenal contents has been found of value in differentiating between benign and malignant causes of jaundice and in localizing the lesions. The important findings may be outlined as follows:

Normal amounts of enzymes with no bile demonstrate that the lesion is in the biliary tract above the ampulla of Vater. If bile appears after repeated instillation of magnesium sulfate solution into the duodenum, it is probable that the obstruction of the biliary tract is benign. The more concentrated the bile obtained, the more probable it is that the lesion is benign. But if bile does not appear, the chance that the lesion is benign is remote.

Abnormal amounts of enzymes with the initial presence of bile or its appearance after intraduodenal instillation of magnesium sulfate solution suggest benign obstruction in the region of the ampulla of Vater, and with the appearance of bile may increase in enzyme concentrations.

Abnormally low enzyme concentrations with persistent absence of bile from the duodenum in spite of repeated intraduodenal administration of magnesium sulfate suggest cancer of the head of the pancreas.

Duodenal contents grossly discolored with blood with abnormal enzyme concentrations and no bile denote cancer involving the head of the pancreas, common bile duct or wall of the duodenum.

In recent years cholangiographic demonstration of the biliary tree is almost routine in some clinics. It can be done during an operation when stones or other abnormalities of the biliary ducts are suspected or postoperatively when the common duct is drained.

During such examination Robins and Jankelson[21] have noted partial or complete filling of the pancreatic ducts in some patients. The ducts are almost always dilated. From their observations they concluded that the filled, dilated ducts are due to some degree of pancreatitis, a point of diagnostic significance.

ANOMALIES AND RARE DISORDERS OF THE PANCREAS

Various anatomic anaomalies of the pancreas have been reported, and the few which are of some clinical importance will be discussed. The head of the pancreas may be annular and surround the descending portion of the duodenum. As a result, compression of the latter may occur and give rise to symptoms of chronic duodenal stasis. Variations in the course of the pancreatic and the common bile duct become of clinical significance when they modify the symptoms. This was exemplified in one of our cases of carcinoma of the head of the pancreas in which intermittent partial obstruction of the biliary tract occurred. At autopsy the common bile duct was so placed that the increasing size of the pancreatic head did not compress the biliary duct but exerted pressure in such a way that it caused the common bile duct to kink and be partially obstructed. In another case the common bile duct was completely obstructed by pressure of the enlarging pancreatic head, although Wirsung's duct emptied below the ampulla of Vater independently of the common bile duct. The remaining anomalies constitute accidental findings. They include accessory pancreas, congenital absence and displacement. Other rare disorders are hypertrophy, atrophy, fatty degeneration, lipomatosis, amyloid degeneration and prolapse. Injuries to the pancreas occur sometimes with its rupture. Among 13,342 autopsies at the Boston City Hospital, miliary tuberculosis of the pancreas was found four times and chronic tuberculous lesions five times. Melanotic sarcoma was found three times, and sarcoma, nesidioblastoma, plasmacytoma and sarcoid each once. No case of syphilitic involvement of the pancreas was found.

ACUTE PANCREATITIS

The term acute pancreatitis as used here includes all those different forms of this condition which are usually classified as separate clinical entities. The reason for the unified classification is that we consider all the various forms as different stages of the same pathologic process. This conclusion is based on observations which are illustrated by the following case of pancreatic edema progressing to acute necrosis:

L. W., a man aged fifty-two years, stated that for six weeks immediately preceding admission he had had epigastric distress, eructations and occasional vomiting. Five hours before admission he was awakened by agonizing, paroxysmal epigastric pain radiating to the left shoulder. Nausea and vomiting also were present. Physical examination showed a well developed and nourished white man, groaning with pain. The extremities were cold, and there was slight cyanosis of the fingertips and lips. The blood pressure was 126 systolic and 82 diastolic. The heart was not enlarged, but at the apex there was a blowing systolic murmur. The lungs showed medium rales in both bases. The abdomen was scaphoid, with boardlike rigidity, and there were generalized exquisite tenderness and rebound tenderness in the right upper quadrant. The temperature was 100 F., the pulse rate 100 and the white blood count 11,700 per cubic millimeter.

The patient was operated on the morning of admission. A few cubic centimeters of thin yellow fluid was present within the peritoneum. The gallbladder was tense and distended, and two small stones were found in the cystic duct. The head of the pancreas was enlarged and edematous. There was also some edema of the transverse mesocolon. No fat necrosis was seen. Cholecystotomy was performed. Postoperative pneumonia developed, and death occurred four days later. At autopsy an acute pancreatic necrosis with scattered fat necroses of the omentum and transverse mesocolon was found.

Etiology.—The destruction of pancreatic tissue is usually accepted to be the result of intrapancreatic trypsinogen activation. Experimentally a great variety of substances forcibly injected into the pancreatic duct can cause changes like those of acute pancreatitis. Such substances are gastric juice, duodenal secretion, acids, alkalis, formalin, bile, bile acids and various bacteria or their toxins. Since pancreatitis is frequently associated with biliary disease, the theory of bile reflux as the chief cause of trypsinogen activation is an accepted one. The correctness of this view is questioned by the recent finding that the pressure within the pancreatic ducts is much higher than any likely to occur within the biliary tract in either health or disease.[7] Infection by way of the lymphatic vessels, which may result from disease of the gallbladder, or by way of the blood stream, as seen in the rare cases of pancreatitis with mumps or pyemia, have also been assumed to be causes of acute pancreatitis. However, cultures made in the early stages in over 50 per cent of the cases are sterile,[23] while organisms grown late in the disease are logically considered as secondary invaders. Rich and Duff[20] have expressed the belief that metaplasia of the ducts causing obstruction to the flow of the external pancreatic secretions is the mechanism underlying this disease. Possibly a spasm of the sphincter of Oddi or of the pancreatic ducts with dilatation and rupture of small canaliculi and the liberation of activated trypsin may play a role in some cases. Accidental injury to the pancreas, such as may occur by gunshot wounds, crushing injuries or trauma incident to operations in the upper part of the abdomen, rarely causes this disease.

In 50 to 60 per cent of all reported cases of acute pancreatitis and in 78 per cent of our cases there were disease and presumably infection of the gallbladder; frequently stones also were present in the gallbladder, the common bile duct or the ampulla of Vater. On the other hand, pancreatitis occurred in but 6 per cent of our patients who had had the gallbladder removed. Acute pancreatitis also occurs spontaneously during or after operation for penetrating gastric and duodenal ulcers. Because of these observations, pancreatitis is considered a secondary disease. Since acute pancreatitis is more likely to occur two or three hours after ingestion of a hearty meal or over-indulgence in alcohol,[18] these should be considered as contributory factors.

Although pancreatitis is reported to be more fequent in men,[10] in our series it occurred twice as often in women. In this series the age varied from nineteen to seventy-three; 50 per cent of the patients were between forty and sixty years of age.

Pathology.—The early stage is that of glassy edema of the gland and frequently of the mesocolon. As a rule, there is no fat necrosis, but a small quantity of serous fluid may be present in the greater or lesser peritoneal cavity. As the condition progresses, there develop the inflammatory manifestations, hyperemia, edema and leukocytic infiltration, and hemorrhagic and necrotic changes. At this stage the entire pancreas or the affected portion of it is enlarged and edematous; the surface presents a mottled appearance, and the consistency may be hard or friable. The color is dark red, purplish or black, and the cross section shows a marbled surface. As the pathologic process advances, diffuse suppuration, localized abscesses or gangrene with sloughing may develop. Accompanying acute pancreatitis there is a variable amount of fat necrosis. With mild involvements the fat in and about the pancreas is involved. With severe disease necrosis is found also in the fat of the omentum, mesentery, abdominal peritoneum and retroperitoneal spaces. Depending on the stage of the pathologic process, there will be thin yellow, chocolate-colored or bloody fluid within the peritoneal cavity.

The pathological changes described may heal with *restitutio ad integrum* or result in various chronic complications, including chronic pancreatitis, single or multiple chronic abscesses and cyst formation.

Symptomatology.—Preceding the onset of acute pancreatitis, chronic upper abdominal complaints are frequent, having been present in 66 per cent of our patients. These symptoms were characteristic of gallstone colic in 38 per cent, of peptic ulcer in 4 per cent and of unclassified indigestion in 18 per cent, while cholecystectomy had been performed in 6 per cent. Thirty-four per cent gave no history of preceding digestive symptoms. The onset is announced by pain, always severe and at times excruciating. It is usually persistent or less frequently paroxysmal and colicky, simulating that of gallstone colic. Much less often the pain is intermittent or occurs in waves similar to those produced by intestinal obstruction. It begins usually in the epigastrium, less often in the right upper abdominal quadrant or rarely diffusely over the abdomen. The radiation of the pain is variable. The most frequent site of radiation is through to the dorsolumbar portion of the back. Other regions are the sternum, either lower abdominal quadrant, either flank and the right or rarely the left or both scapulas. In our series of patients radiation to the left upper abdominal quadrant rarely occurred. Nausea and vomiting develop almost simultaneously with the onset of pain. The vomitus at first contains food, but soon becomes bilious. Hematemesis was observed by us in one case. Constipation is the rule. With moderately severe disease the pulse rate is usually 80 to 90 and the temperature between 99 and 101 F., although occasionally normal and rarely subnormal. With severe involvement there rapidly develops circulatory collapse characterized by pallor, cyanosis or lividity of the face, cold extremities, clammy skin, slight and rapid pulse, falling blood pressure and subnormal temperature. According to Brown,[4] collapse is due to toxemia; Rowland,[22] however, explained it as the result of hypoglycemia. However, hypoglycemia was not observed in any of our patients; in fact, 14 per cent of them showed hyperglycemia and glycosuria on admission to the hospital. When suppuration or gangrene of the pancreas develops, the pulse rate often rises to between 120 and 140, and the picket fence type of temperature curve commonly occurs. On physical examination the patient with acute pancreatitis appears to be acutely ill. The abdomen is usually distended or scaphoid. While there are more or less upper abdominal spasm and tenderness, in only about 35 per cent of our cases were there exquisite tenderness in the upper part of the abdomen and marked muscle spasm in the epigastrium or over the gallbladder. The spasm is seldom sufficient to present boardlike resistance to palpation. A palpable mass is rarely found. Jaundice was present in 24 per cent of our cases. It was due to the associated cholecystitis with stones, cholangitis or pressure on the common duct by the swollen and enlarged head of the pancreas. Even with severe disease the sensorium remains clear.

Detection of the evanescent rise in the diastase or of the much more persistent increase in the lipase of the blood is of suggestive diagnostic value. While the leukocyte count may be normal, it is frequently elevated to between 10,000 and 15,000 and with severest involvement may reach 22,000 per cubic millimeter. In our cases with jaundice the icteric index varied from 14 to 75. The urine shows bile pigments in the presence of jaundice. Urinary diastase has been reported to be increased during the first twenty-four to forty-eight hours after the onset. This observation seems worthy of further investigation.

Diagnosis.—The clinical diagnosis of acute pancreatitis is rarely made with certainty; indeed, even an experienced surgeon may overlook the milder or focal forms during exploratory laparotomy. The usual conditions to be differentiated are perforation of gastric or duodenal ulcer, peritonitis, acute cholecystitis, cholelithiasis, intestinal obstruction and mesenteric thrombosis or embolism. In our series of cases perforation of a peptic ulcer was the most common mistaken diagnosis. Aids in the differentiation are the absence in acute pancreatitis of obliteration of liver dulness and of the subdiaphragmatic air bubble demonstrable on the *x*-ray film of the abdomen when the patient is in the erect or sitting position. Furthermore, the spasm and rigidity of the upper abdominal muscles so characteristic of perforation are lacking in fully two-thirds of the patients with acute pancreatitis; also in this group the severity of the pain is out of proportion to the physical findings. Acute cholecystitis causing the severe pain resembling acute pancreatitis will always give at least localized tenderness in the right upper abdominal quadrant. With acute pancreatitis the patient is more seriously ill and may even be in shock. There is often some glycosuria. Unless peritonitis is of chemical origin, as occurs with perforated peptic ulcer, the pain is not of sudden onset and is not nearly so severe as that of acute pancreatitis. Furthermore, glycosuria, jaundice and elevation in blood diastase and lipase values are not symptoms of peritonitis. Although the following findings are somewhat variable, they furnish aids in differentiating intestinal obstruction from acute pancreatitis: inability to pass flatus and feces even after enemas, well marked distention of the abdomen, early absence of leukocytosis, normal temperature, presence of fluid levels within the bowels on scout x-ray films and occasional presence of visible peristalsis. Mesenteric thrombosis or embolism shows diminished or absent peristalsis and symptoms resembling those of intestinal obstruction. Also, the passage of bloody or tarry stools may occur. Coronary thrombosis and gastric crisis ought to be considered in the differential diagnosis.

Treatment.—One important prophylactic measure is the proper treatment of gallbladder disease. Concerning the pancreatitis, there is considerable discussion of immediate surgical *versus* conservative treatment. Obviously an absolute diagnosis is presupposed when conservative treatment is the choice. However, since an absolute preoperative diagnosis can rarely be made, immediate exploration becomes necessary except in shocked or moribund patients. When the correct diagnosis of acute pancreatitis is made at laparotomy, the common procedure is to drain the gallbladder or common bile duct. Incision of the capsule or drainage of the pancreas is unsatisfactory. The mortality of immediate operation is from 50 to 75 per cent, depending on the severity of the process. On the other hand, the mortalities reported for conservative treatment vary from but 7.5 to 22 per cent. It is admitted also that spontaneous recovery can occur. However, because diagnosis without anatomic examination of the pancreas is difficult, the correctness of the mortality figures is problematical.

The medical treatment consists of bed rest, total abstinence from orally administered food and drinks, supportive measures to combat shock and circulatory collapse and the parenteral administration of saline or dextrose. Since there may be a disturbance of the calcium and fat metabolism which can account for some of the symptoms, calcium therapy is recommended. Wagensteen[26] and others warned against excessive amounts of dextrose and referred to the work of Babkin, who demonstrated an increase of pancreatic enzyme secretion when the blood sugar is raised. Wagensteen's decompression of the stomach and transduodenal drainage of the pancreas have been recommended in treatment of this disease. We have had no experience with the latter method; however, we question the practicality or feasibility of this procedure particularly for severe disease. One must always bear in mind that recurrent attacks of pancreatitis are common. In fact, one attack predisposes to others, which often are more severe and may terminate fatally. For this reason, contributory lesions, such as diseases of the gallbladder, the presence of stones in the extrahepatic bile ducts and penetrating peptic ulcers, should be properly treated.

CHRONIC PANCREATITIS

Etiology.—Chronic pancreatitis may result from any cause for an overgrowth of connective tissue. Among these are disorders of the parenchyma, such as carcinoma, acute pancreatitis, inflammations caused by a penetrating duodenal ulcer and pancreatic calculi. A second common cause is benign or malignant occlusion of the pancreatic duct. It also accompanies chronic disease of the liver or gallbladder and generalized arteriosclerosis. Among the 36 autopsies at the Boston City Hospital, gross cirrhosis of the liver was present in 7 cases and microscopic in 8, chronic cholecystitis in 12, cholelithiasis in 7 and generalized arteriosclerosis in 27. Because of its relation to cirrhosis of the liver, alcohol is generally considered a causative factor, as is ascending infection from the bile duct or the duodenum.

Pathology.—Chronic pancreatitis is characterized by an increase in the connective tissue stroma. Morphologically it may be divided into interlobular and intralobular types. However, the sclerosis becomes of clinical importance only when the ducts have become so occluded or the glandular cells so degenerated that the quantity or quality of pancreatic juice is seriously diminished. Also a progressively advancing sclerosis may eventually affect the islands of Langerhans and produce diabetes mellitus. Of the 36 autopsies, 5 were of patients who had had diabetes mellitus for eight to fifteen years. Nevertheless, the extensive sclerosis demonstrated was no different from that in many of the other 31. Thus, the role played by the sclerosis in causing the diabetes in these patients is problematical.

Symptomatology.—Whether chronic pancreatitis in the absence of gross hypochylia causes demonstrable symptoms is problematical. The essential reason for this is that the symptoms occurring in its presence are more logically attributable to the organic diseases with which it is invariably associated. That minor pancreatic disturbances do not give rise to demonstrable symptoms is discussed in this section on hypochylia. Furthermore, after complete exclusion of pancreatic juice from the intestines, fats are split into fatty acids, and much absorption of both the fats and the proteins of the food may occur.[17] Thus, in the absence of creatorrhea the proper duodenal enzyme studies furnish the one clinical means by which the presence of chronic pancreatitis may be detected. Rarely, as a result of the sclerosis little or no pancreatic juice enters the intestines. Under such circumstances proper studies of duodenal contents will demonstrate the presence of few or no pancreatic enzymes. Such findings were made in one of our cases, in which the chronic pancreatitis was the end-result of an acute hemorrhagic necrosis. In such cases the stools are frequent, bulky and grossly fatty. They contain large amounts of well preserved muscle fibers. For this reason the nucleus test of Schmidt is of diagnostic value. As suggested previously, the occurrence of diabetes mellitus as a symptom of chronic pancreatitis is difficult to evaluate.

Diagnosis.—The diagnosis of pancreatitis becomes of importance in some cases of sprue and those unusual cases of mesenteric adenopathy in which fatty stools occur in the absence of jaundice.[2] The proper duodenal enzyme studies furnish the deciding factor in the diagnosis. In those very rare cases in which chronic pancreatic sclerosis produces icterus, all other causes for jaundice are to be considered in the differential diagnosis.

Treatment.—Prophylactic measures consist in the proper treatment of diseases of the gallbladder and bile ducts and of the liver, peptic ulcer, duodenitis and gastritis, and also abstinence from alcoholic beverages. These same prophylactic requirements are to be fulfilled in the rare cases of chronic pancreatitis which can be diagnosed. In that condition the effects of malnutrition due to the lack of pancreatic juice are to be combated. Because they are most easily assimilated, carbohydrates should constitute the major portion of the diet. The amount of meat allowed can best be governed by microscopic examination of the stools to determine the degree of creatorrhea. The protein requirement may be aided by feeding preparations of aminoacids, such as aminoid compound. Fats are to be largely eliminated. Care should be taken that the diet contains suitable amounts of minerals and vitamins. Raw, finely ground pancreas served with salt may be given with the meals in the largest amounts which the patient can tolerate. A demonstrably active preparation of pancreatic enzymes may be administered in large doses. In such doses it may be followed by conspicuous clinical benefit and by a significant decrease in the amount of fat and nitrogen excreted in the feces.[19] When diabetes is a complication, insulin therapy is essential. If jaundice is present, appropriate surgical measures are to be given consideration.

FUNCTIONAL PANCREATIC HYPOCHYLIA

The occurrence of minor functional pancreatic hypochylia has been established in the presence of various diseases.[16a] As in these conditions at least some sclerotic changes invariably occur in the pancreas, the hypochylia cannot be correctly considered to be of purely functional origin. Furthermore, the accompanying diseases mask any role the hypochylia may play in the symptomatology. In the published reports describing symptoms attributed to pancreatic hypochylia neither the presence of hypochylia nor the absence of pancreatic disease has been incontrovertibly established. Thus, at present the clinical status of so-called functional pancreatic hypochylia is problematical.

CARCINOMA OF THE PANCREAS

Carcinomas of the pancreas constitute 1 to 2 per cent of all carcinomas of the human body and are more frequent in the male sex. They may be primary or secondary. The latter type is relatively rare and is usually the result of direct extension from neighboring organs, chiefly the stomach. Primary carcinoma of the pancreas may begin in any part of the organ, but the head is the most frequent site of origin. In the later stages the entire gland may be so involved that the site of origin cannot be determined. Histologically, it develops from either ductal or acinar epithelium, and three forms can be differentiated, the scirrhous, the medullary and the rare colloid.

The carcinoma may spread by metastasis or by direct extension. The most frequent sites of metastatic lesions are the regional glands and the liver. Extension into the retroperitoneal space is common. By direct extension the duodenum, the ampulla of Vater and the common bile duct may be invaded. The stomach, the left kidney or ureter, the bladder and the colon have been the seat of secondary cancerous involvement. Distant metastases occur and may involve the lungs, pleura, diaphragm, peritoneum, vertebrae and various lymph nodes. Pressure of the enlarged pancreas on neighboring organs may give rise to symptoms comparable to those of cancerous invasion. The inferior vena cava and splenic or portal veins may be compressed by carcinomatous enlargement of regional glands or rarely may be invaded by cancer cells.

Regarding the etiology of primary carcinoma of the pancreas suffice it to say that, as for carcinoma in general, the question of chronic irritation has been raised. Although changes characteristic of chronic pancreatitis are seen histologically in cancer of the gland, whether these changes predispose to malignant transformation or are the result of a preëxisting carcinoma has not been established. Primary disease of the gallbladder in association with carcinoma of the pancreas occurs more commonly than is generally recognized. In a recent study of 50 consecutive primary carcinomas of the pancreas, we have found gallstones eight times and a shrunken or thickened gallbladder without stones twice. In one case the gallbladder had been previously removed because of chronic cholecystitis.

Symptomatology.—The patient's presenting complaint is usually (*a*) obstructive jaundice or pruritus; (*b*) loss of weight and appetite, fatigability and weakness, or (*c*) "indigestion." The last includes symptoms varying from epigastric distress or a sensation of fulness and belching to epigastric or left hypochondriac pain. The pain is at first mild, but often becomes severe later. It may radiate into the left flank, lumbar part of the back or lower left part of the chest. However, pain may be absent throughout the course of the disease. If one examines a patient without jaundice in this early stage, usually nothing abnormal is found on either physical or roentgen examination. We know of cases in which because of this lack of positive findings an erroneous diagnosis of gastric neurosis or arthritis of the spine was made. During this stage one may suspect a malignant growth, but it is impossible to make a diagnosis. The earliest objective, although not diagnostic, evidence we have observed is marked diminution in the fat-splitting enzyme of the duodenal contents.

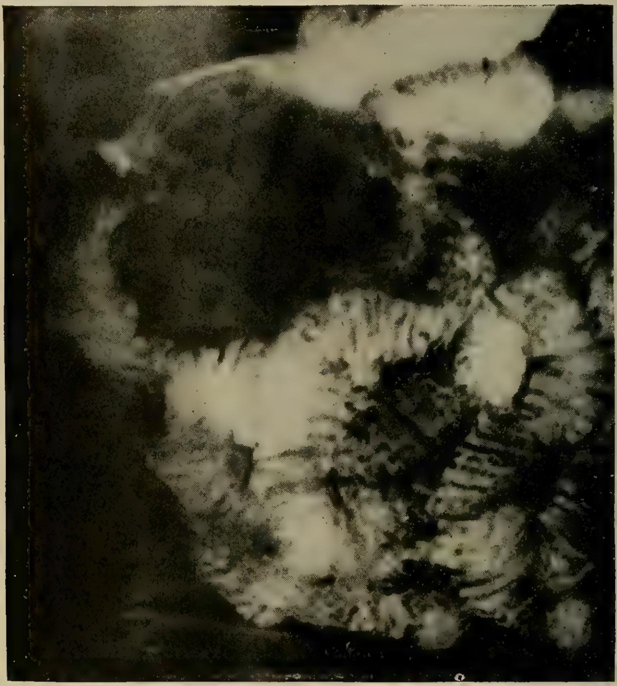

Fig. 94.—Carcinoma of the head of the pancreas. Note the displacement of the duodenal loop and the pressure on the greater curvature of the stomach.

As the growth increases in size or extension occurs, other signs and symptoms develop. Since in the majority of cases the head of the pancreas is involved, jaundice of the complete obstructive type develops sooner or later, often with a pruritus which may be very annoying to the patient. Jaundice was present in 82 per cent of our cases. Although it is usually described as painless and persistent, many exceptions occur. If one thinks only of the colicky pain seen with gallstone obstruction of the common bile duct, then pain is indeed rare. However, a variable amount of pain described by the patient as boring or burning is not infrequent. This is evidenced by the finding of at least some pain in 70 per cent of our cases. The jaundice is usually completely obstructive, with no bile in the stools and no urobilinogen in the urine. However, we have observed cases in which the bilirubinemia fluctuated within a wide range as well as cases in which traces of bile in the stools and of urobilinogen in the urine appeared intermittently. These findings indicate that neither the jaundice nor the complete obstruction of the biliary tract is always persistent. The red blood cell count usually varies from 3,000,000 to 4,000,000 per cubic millimeter and the hemoglobin concentration from 60 to 80 per cent.

When the site of malignant change is the body or the tail of the pancreas, jaundice is characteristically absent throughout the course of the disease. In such cases pain may be the only symptom. It may resemble the pain of gallstone colic or it may be persistent, and it may be aggravated by change of position of the patient. Nausea and vomiting are common complaints. Changes in bowel habits, such as constipation or more rarely diarrhea, may develop, suggesting primary malignant disease of the large bowel.

On physical examination in the earlier stages, the patient may appear in good to fair health. As the disease advances there occur progressively increasing weakness, asthenia and emaciation. When present, unless very early, jaundice is deep and may have a greenish tinge. Bradycardia is exceptional. Evidence of scratching as a result of pruritus is frequent. The liver is palpably enlarged in over 50 per cent of cases. This enlargement is due to biliary cirrhosis or metastases. Although at autopsy or operation the gallbladder was distended and enlarged in 70 per cent of our cases with jaundice, it was palpable in but 15 per cent of them. When palpable, the gallbladder is nontender and almost invariably mobile and feels smooth, globular and cystic. These findings help to differentiate it from an enlarged lobe of the liver or a carcinoma of the gallbladder. Occasionally an epigastric mass is palpable and is apt to feel nodular or irregular on palpation. It is placed deeply within the abdominal cavity, where it does not move with respiration. It may be mistaken for a tumor of the stomach or colon. Tenderness on deep palpation may be present even in the absence of a tumor.

The stool in the presence of jaundice is acholic and fatty. Occult blood in the stools is variable. When present persistently, it suggests invasion of the ampulla of Vater or duodenum or a primary carcinoma of the extrahepatic bile ducts. In the presence of icterus, the urine contains bile pigment, bile salts and frequently a trace of albumin, but urobilinogen is usually absent. Excepting such fluctuations as have been noted, the jaundice is marked by a persistent hyperbilirubinemia. In most cases observed by us there was no marked deviation from normalcy in either the clotting or the bleeding time. Prothrombin is often diminished. The absence of bile on transduodenal drainage is an important finding strongly suggestive of carcinoma of the head of the pancreas, as discussed previously. The roentgen film occasionally shows evidence of extrinsic pressure on the stomach or duodenum. Glycosuria and hyperglycemia were present in 5 of our 50 consecutive cases. However, in only one of these was the diabetes attributable to the carcinoma of the pancreas. Thus, diabetes mellitus is not a common symptom of cancer of the pancreas.

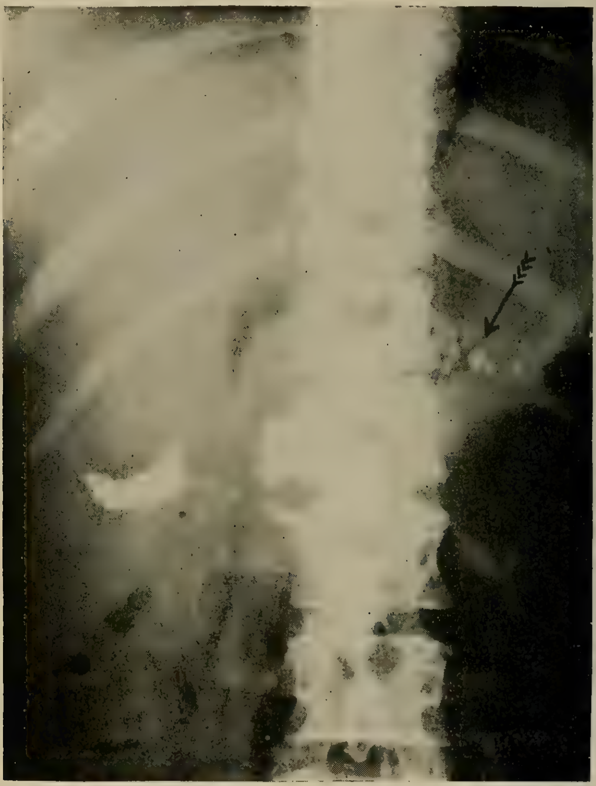

Fig. 95.—Multiple calculi of the pancreas, to which the arrow points. In the original film some stones were visible also over the spine.

Differential Diagnosis.—The differential diagnosis of carcinoma of the pancreas is governed largely by the presence or absence of jaundice. This in turn involves the differential diagnosis between obstructive and intrahepatic jaundice, which is discussed in another chapter of this volume. In the majority of cases, jaundice due to calculous obstruction of the common bile duct can be differentiated. However, there are some lesions of the so-called silent stone type which simulate malignant obstruction. With such lesions a sustained increase in serum lipase points to cancer.[8]

Cancer of the pancreas unaccompanied by jaundice can usually be differentiated from cancer of the stomach or of the large bowel by radiographic and gastroscopic observation. Unless demonstrably of secondary origin, malignant involvement of the retroperitoneal glands may rarely simulate cancer of the pancreas. Chronic pancreatic abscess may become palpable and simulate a new growth. However, it is less apt to cause the severe degree of asthenia and emaciation. Cysts, such as the omental and the pancreatic, are largely differentiated by the physical findings. Especially important are mobility and fluctuation. In the rare cases in which chronic pancreatitis or mesenteric adenopathy suggest cancer the proper duodenal enzyme and bile studies may aid in the differential diagnosis.

Treatment.—The only treatment which alleviates symptoms and prolongs life is surgical. One important prophylactic measure in the proper preparation of the jaundiced patient for operation is to increase the glycogen content of the liver through the administration of dextrose orally or intravenously. The danger of postoperative hemorrhages may be lessened by such measures as blood transfusions and the oral administration of vitamin K together with bile salts, or vitamin K may be given intramuscularly or intravenously. The operation of choice is cholecystogastrostomy or cholecystojejunostomy as a palliative measure. Either relieves the jaundice and the pruritus and probably prolongs the life of the patient. Recently a two stage operation involving first the drainage of the gallbladder and then the anastomosis was recommended by Walters[25] and Lahey.[15] Recently, too, Whipple[28] has attempted to extirpate the cancerous pancreatic tissue. So far the mortality of the Whipple operation is about 40 per cent or more, and radical cures have not as yet been reported. The results of animal experiments suggest a possible danger of fatty degeneration of the liver following this operation. This can probably be prevented by the administration postoperatively of a diet high in lecithin or of choline or "lipocaic."[9]

The medical management consists of symptomatic treatment, including the use of opiates to control pain. The dietetic management is guided by those principles outlined in the treatment of chronic pancreatitis. Recently *x*-ray therapy has been tried, with questionably beneficial results.

PANCREATIC CALCULI

Pancreatic stones are rarely diagnosed clinically, as was shown by Bost,[3] who collected 107 cases of pancreatic calculi, in but 4 of which the diagnosis was made preoperatively and in only 24 during laparotomy. How readily pancreatic stones may be overlooked even during operative inspection of the pancreas is illustrated by the following case:

E. W., a man aged fifty-four years, was admitted to the Boston City Hospital complaining of severe upper abdominal pain and vomiting. Three weeks before admission dull epigastric pain developed, becoming progressively more severe and colicky. This had become especially severe in the preceding two weeks. It radiated mainly to the right axilla, back and right flank, and to a lesser degree to the left midclavicular line and upward to the third rib. The pain was accompanied by vomiting, more marked after meals. On palpation there was mild tenderness over the gallbladder region. The white blood cell count was 13,000 per cubic millimeter.

On laparotomy chronic cholecystitis without gallstones and slight enlargement of the head of the pancreas was found. Eighteen days later the patient died of acute heart failure, and at the autopsy multiple small soft stones were found in the pancreatic ducts and within the parenchyma.

Pancreatic stones occur in both sexes, most commonly between the ages of forty and sixty. They are usually multiple, smooth, rounded or oval and rarely faceted. Their most frequent site is the duct of Wirsung within the pancreatic head, but they have been found also in the parenchyma, in cysts and in abscesses of the pancreas. Their formation is presumably the result of either infection or pancreatic metabolic disturbances. A causal role of the latter is suggested by the observation that the calculi are composed of calcium phosphate and carbonate, although the pancreatic secretion normally contains insignificant amounts of these salts. Accompanying and probably secondary to the stones is a variable degree of chronic pancreatitis.

Symptomatology.—Symptom-free, or silent, pancreatic calculi occur. They may be unexpectedly found on the *x*-ray film or during laparotomy, but are more frequently discovered at autopsy.

Pancreatic calculi may give rise to attacks of paroxysmal colicky pain simulating gallstone colic. However, the pain is apt to differ somewhat in location and distribution. Although epigastric, it is usually located along the left rather than the right costal boundary of the epigastrium, and it radiates to the left side and back rather than to the right. The attacks of pain are frequently accompanied by nausea and vomiting and occasionally by glycosuria. Rarely jaundice may develop as the result of occlusion of the ampulla of Vater. Much more rarely a stone composed of calcium and free from bile constituents has been recovered from the stools. Between attacks there are frequently dull pain and variable tenderness in the epigastrium, together with the symptoms commonly termed gastric dyspepsia. However, whether these symptoms are the result of the pancreatic calculi or of commonly associated diseases such as cholecystitis is not established.

The colic of pancreatic calculi is usually mistaken for that due to cholelithiasis. The diagnosis includes (*a*) attacks of epigastric pain, (*b*) elimination of other causes for epigastric pain and (*c*) demonstration of shadows of the opaque calcium stones on roentgen film. The last may be imitated by the shadows of calcified lymph nodes in the anatomic region of the pancreas. The occurrence of attacks of epigastric pain followed by recovery from the stools of calcium stones uncontaminated with bile constituents suggests the diagnosis.

Treatment.—Usually the diagnosis of pancreatic lithiasis will be made only on careful exploration of the pancreas during laparotomy. However, when the clinical diagnosis is suspected, the operative removal of stones is indicated in the presence (*a*) of attacks of pain, (*b*) of jaundice or (*c*) of obstruction to the flow of pancreatic juice, evidenced by diminution of enzymes in duodenal contents. Furthermore, their removal prevents the development or aggravation of chronic pancreatitis. The palliative treatment of pancreatic colic is similar to that of biliary colic, discussed elsewhere in this volume.

CYSTS OF THE PANCREAS

Cysts of the pancreas occur with approximately equal frequency in both sexes. Although they are usually seen in middle-aged patients, our youngest patient was nine months and the oldest eighty-seven years old.

Etiology.—Cysts of the pancreas are rare.[24] Their infrequency is illustrated by the observation of only 10 pancreatic cysts in 13,342 autopsies and but 4 during operations at the Boston City Hospital. Although their origin is not well understood, cysts follow obstruction of the pancreatic ducts, inflammations such as acute pancreatitis and trauma. Four of the 10 pancreatic cysts found at autopsy were associated with congenitally cystic kidneys. Pancreatic cysts are usually filled with liquid, which is colorless or discolored by changed blood. One small cyst of the Boston City Hospital series contained yellowish pasty material composed of cholesterol, and another a fatty substance. A third contained a gelatinous substance resembling mucus, and a fourth, very large cyst was filled with clotted blood forming a hematoma.

Pathology.—Pancreatic cysts are either unilocular or, less often, multilocular. The wall is composed of fibrous tissue, which may be lined with cuboidal or columnar epithelium. They vary in size from microscopic lesions to one described as of the size of a fetus at term. For clinical purposes they may be classified as benign, including echinococcic, and malignant. The latter two types are much the rarer.

Symptomatology.—In one of our patients distention of the abdomen was the only symptom. In another, persistent vomiting and a sensation of abdominal weight were the only complaints. In 2 patients the cystic mass was palpable in the left upper quadrant of the abdomen, where severe pain was localized in one, while in the other severe colicky pain was confined to the left lower quadrant. Pain is the most constant symptom of pancreatic cysts. It varies greatly in severity and character. It may be mild or so severe as to lead to collapse. It may be persistent or of the paroxysmal, colicky type. It is usually located in the epigastrium or left hypochondrium, from which it may radiate to the dorsolumbar part of the back. However, the pain may be located in the right hypochondrium, where it has been described as resembling that of gallstone coli..[24] Vomiting frequently accompanies the pain. Large cysts may exert pressure on adjacent organs. This is illustrated by the *x*-ray finding in one of our cases, that the "lesser curvature of the stomach was impinged upon by a huge rounded smooth mass which crowded both curvatures of the stomach together and in turn compressed the stomach against the left lateral wall of the abdomen." The pressure of the cyst on the stomach may lead to gastric disturbances, such as anorexia and vomiting, and on the intestines, to both partial and complete obstructions. Pressure on the common bile duct may cause jaundice. When the vena cava is compressed, ascites develops. Sufficient destruction of pancreatic tissue may cause pancreatic hypochylia, diabetes or both. Loss of weight and asthenia, which may be extreme, are common symptoms. Sometimes these symptoms result from anorexia and vomiting, while at other times no explanation is obvious.

Physical examination may give negative results or may show a mass in the left epigastrium, left hypochondrium or both. Rarely the mass occupies the right epigastric and hypochondriac regions or the whole abdomen. The tumors vary greatly in size, and 4 of those in our series varied on palpation from one about 15 centimeters in diameter to one which filled the entire abdomen. The mass is usually smooth, rounded, firm or hard. However, it may impart a sense of elasticity to the palpating hand, and in some cases fluctuation has been obtained. Not infrequently the cystic tumor mass is movable. One of those in our series was a large multilocular cyst occupying the left upper part of the abdomen. On palpation it presented a hard mass composed of smooth nodules. The spontaneous disappearance of a cystic tumor has been reported, and the assumption is that the cyst ruptured into the peritoneal cavity or the intestine.

Pancreatic cysts are closely resembled or simulated by those of the mesentery, mesocolon or omentum. However, since pancreatic cysts may occupy any part of the abdomen, they may be confused with cysts originating in the liver, spleen, kidneys, ovaries, retroperitoneal tissues and adrenal glands. A hydronephrosis or a distended gallbladder also may resemble a pancreatic cyst. Physical findings aiding in distinguishing tensely distended cysts from solid tumors of the pancreas or of retroperitoneal structures are the spherical shape and smooth surface of the former.

The treatment is surgical. Marsupialization is the usual operation, but extirpation may be accomplished.

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PART IV

The Small and Large Intestine

CHAPTER XXI

THE PHYSIOLOGY OF THE SMALL AND THE LARGE BOWEL*

Digestion.—Digestion in the intestine is due mainly to the ferments of the pancreatic and intestinal juices. The bile aids the digestion of fat and increases the activity of some of the enzymes.

Duodenal juice, the juice collected from fistulæ of the Brunner's gland area, is clear, either colourless or faintly yellow. The deposit is often appreciable and when present consists of grayish mucin (probably from goblet cells of the villi) and cell debris, for the most part of unrecognizable origin though much of it may be epithelium. Bacteria are often present. The specific gravity varies between 1,007 and 1,009. The juice is mucoid and the degree of stickiness varies from species to species. All the secretions had an alkaline *p*H (rabbit 8.0 to 8.2).

Amylase and enterokinase are constantly present. The alkalinity and high mucin content of duodenal juice suggest that the secretion may protect the delicate villi of the first part of the intestine from the damaging action of the ejected stomach acid contents. It has also been stated that the "intrinsic factor" is present in the juice. Although it is impossible to say definitely what are the contributions of Brunner's glands and of the villi and crypts of Lieberkühn, there is good reason for believing that Brunner's glands are responsible for a large part of the secretion and that mucin is their product. Florey, Wright and Jennings.[25]

Typical duodenal mucoid juice can be collected without subjecting the fistula to mechanical stimuli. Fistulæ of other parts of the intestine will, except for small amounts of periodic juice, only produce fluid after some form of local stimulation.

The pancreatic juice is a clear alkaline fluid with a *p*H about 8 and contains trypsinogen, erepsin, lipase, amylase, a trace of maltase, protaminase and other organic substances. The inorganic material consists mainly of sodium, chloride and bicarbonate ions.

According to Berk *et al.*[11] the effective acidity of the duodenal contents is largely determined by the type of food undergoing digestion and only partially by the acidity of the gastric contents.

It is usually stated that the intestinal juice is secreted by the crypts of Lieberkühn but the function of the component cells of the intestinal mucosa is not known. It has not been settled whether the crypts secrete and the villi absorb or whether they have a common function, as the common origin of their epithelial covering suggests, in which instance both crypts and villi would secrete and absorb.[25]

Fistula juice consists of two parts—a watery supernatant fluid and a clumpy or floccular part. The fluid is slightly yellow, clear or opalescent; has an aromatic smell and an alkaline reaction. The floccules are mainly composed of mucus with which are mixed degenerating epithelial cells, microörganisms and cholesterol crystals.[25]

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*The general histology and neurology are covered in Dr. De Garis' chapter.

Normal human jejunal juice collected by means of a Miller-Abbot tube tends to have a characteristic acid-base balance with a bicarbonate concentration, about one-third of the blood serum, and a carbon dioxide tension about double that of the venous blood resulting in a pH of 6.5.[55]

The juice contains a large and varied array of enzymes, including erepsin (polypeptidase and peptidase), lactase, maltase, invertase, lipase, phosphatase, nucleinases, nucleotidases and nucleosidases. Enterokinase, which is also present, is not, as was formerly supposed, an enzyme, but a coenzyme. Owles[65] has suggested that in man invertase, erepsin and lipase are true secretions.

The intestinal juice has significant and varied digestive powers. The amount of digestion by the enzymes appears to run parallel with the cell content of the juice suggesting that these enzymes are derived from cast off epithelial cells rather than from the mucosa by secretion. It has been suggested that they exert the most important part of their digestive function during absorption.[25]

On passing to the duodenum, undigested and partially digested carbhydrates are acted on by the amylase of the pancreatic juice. This enzyme has a similar but more powerful action than ptyalin. Pancreatic amylase, unlike ptyaline, acts on unboiled starch. The optimum pH for the enzyme is 6.7. Certain inorganic ions, especially the chloride ion, accelerate its action.

The enzymes maltase, invertase and lactase present in the intestinal juice act on maltose, sucrose and lactose and convert them into monosaccharides. A molecule of maltose is converted by maltase into two molecules of dextrose by a process of hydrolysis. Small amounts of maltase are present in the pancreatic juice. Sucrose is split into a molecule of dextrose and of fructose by invertase. Lactase converts lactose into dextrose and galactose. The hydrolysis of the glycolipids, certain proteins and glycosides also results in the liberation of various sugars.

On leaving the stomach, the acid mixture of proteoses, peptones and acid metaproteins is practically neutralized in the small intestine. Trypsin carries the digestion of proteins beyond the peptone stage. The enzyme trypsin, which is formed by the interaction of trypsinogen and enterokinase, is a mixture of several proteolytic enzymes which act in different ways on different substrates. The specific action of trypsin is to break the proteoses and peptone fragments of the protein molecule into smaller amino acid groups, "peptids." Some of these contain two, three or four amino acids, constituting di, tri and tetra peptids. Some individual amino acids may be set free. The peptids are acted on by erepsin and converted into amino acids. Anderson[5] has reported that the assay of trypsin in duodenal contents is a reliable means of assessing pancreatic deficiency.

The intestinal juice contains also nucleinases, nucleotidases and nucleosidases. Nucleinases hydrolyze nucleic acids into their constituent nucleotides; the nucleotidases split the nucleotides into nucleosides and phosphoric acid; the nucleosidases separate the nucleosides into monosaccharides and purine bases.

Fats are hydrolyzed in the small intestine by the lipase of the pancreatic and intestinal juices and the fat molecule is split into its constituent fatty acids and glycerol. It is frequently stated that fatty acids combine with the alkali in the intestinal fluids to form soaps. This statement is discussed later. Enzymes present in the small intestine are activated after secretion by bile and other agents. Bile is essential for the efficient digestion and absorption of fat, yet the bile contains no digestive enzymes.

Bile owes its importance in digestion to its peculiar properties: 1. Bile salts act as specific activators of lipase. 2. Bile aids emulsification, reducing the fat globules in size, and a more stable emulsion results. 3. Bile salts also aid absorption by rendering substances water-soluble. This latter action of bile is due to the property possessed by the bile acids of lowering surface tension and of forming hydrotropic compounds. Many substances such as fatty acids combine with desoxycholic acid to form compounds called "choleic acids." In this way insoluble fatty acids, cholesterol and the fat-soluble vitamins are rendered water-soluble and diffusible and are therefore capable of being absorbed.

In addition, bile aids in the neutralization of the acid gastric juice, and the bile salts reabsorbed from the small intestine act as cholagogs.

Fat digestion can be carried on after ligation of the bile ducts, but then over 80 per cent of the food fat is found in the feces in the form of fatty acids and soaps. The absence of bile would therefore inhibit the absorption of fat. According to Shapiro *et al.*[73] 65 to 70 per cent of the fatty acids may be absorbed in the absence of bile: the increase of fecal fat in the absence of bile being due to the fats secreted into the intestinal lumen.

The epithelial lining of the crypts of the cecum and colon is composed of large numbers of goblet cells interspersed between clear protoplasmic cells. The juice collected from cecal and colonic fistulæ varies from clumps of white mucus to an almost watery fluid. It is viscous and opalescent with mucus distributed unevenly through it. The juice has an alkaline reaction. The enzymes, amylase, invertase, lipase, peptidase have been reported to be present but it is doubtful if any actual secretion of enzymes occurs. Mucus is the most important constituent. The mucoid fluid can apparently be reabsorbed, the colonic mucosa thereby maintaining a layer of mucus on its surface: the thickness of the layer is varied by secretion and reabsorption according to local needs.

Mucus lubricates the solid feces and also binds the fecal particles. Again if the feces contain irritant material, fluid is produced which protects the mucosa by diluting the irritant and blocking diffusion. The alkaline content of the secretion is considerable and may neutralize acids produced by bacterial action.[25]

CONTROL OF SECRETION

The Role of the Gut in Pancreatic Secretion.—The secretion of pancreatic juice is under the control of a nueral and a hormonal mechanism. In 1902 Bayliss and Starling[9] showed that a flow of pancreatic juice occurs when the acid gastric chyme enters the duodenum. These observers were also able to demonstrate that pancreatic secretion follows the introduction of acid into the jejunum after section of all the nerve connections. It was therefore suggested that the acid acted by liberating some chemical substance (secretin) which passed into the blood stream to reach the pancreas.

Mellanby and Huggett[62] in 1926 demonstrated that secretin exists in the intestine in a preformed state in the mucosa. Mellanby[60] later proved that bile is a much more potent stimulus than acid and that the active agent is the cholic acid of the bile. The highest concentration of secretin is obtained from the duodenum and the upper part of the jejunum (Mellanby[61]).

The enzyme output of the pancreas does not depend solely on a nervous control, for Harper and Vass[38] found that the passage of food stuffs or water through the pylorus into the duodenum resulted in an increase in the enzyme output by the pancreas even when all the extrinsic nerves to the small intestine had been cut. These observers also showed that secretin had no stimulant action upon the output of enzymes. More recently Harper and Raper[37] have extracted a substance from the small intestine "pancreozymin" which on intravenous injection into cats causes an increased secretion of enzymes by the pancreas but has no effect on the volume of juice secreted. The action of pancreozymin, which can be separated from secretin, is unaffected by the section of the extrinsic nerve.

These results probably explain the observations made by Thomas and Crider[79] that the products of protein digestion acted in the intestine as stimuli for the secretion of pancreatic juice. Ivy[44] has also shown that the nature of the foodstuff ingested influences the enzyme content of the secretion.

The entrance of chyme into the small intestine therefore causes a secretion of pancreatic juice through: (1) the liberation of secretin from the mucosa; (2) the effect of the chyme on the flow of bile, which in turn increases the absorption of secretin into the blood, and (3) the liberation of pancreozymin. It is also possible that the passage of the gastric contents into the duodenum may stimulate afferent nerve endings which bring about a reflex secretion of pancreatic juice.

Duodenal Juice.—Florey and Harding,[23,24] have been able to confirm Ponomarew's[67] original observations that the presence of diluted HCl in the intestine caused a secretion of juice. Again when animals were deprived of food for twenty-four hours the fistulæ ceased to secrete but within a few minutes of taking food a mucoid juice began to flow. The same phenomena has been demonstrated in the duodenum which had been transplanted subcutaneously and deprived of all nervous and vascular connections with the abdominal contents. Highly purified secretin injected intravenously in the cat caused typical secretion from a quiescent fistula.

In addition to hormonal control there appears to be a sensitive acetylcholine mechanism which can be set in action by vagal stimulation, by the removal of a sympathetic nerve inhibition or by paralyzing the esterase with eserine.

Nassett[63] is of the opinion that the fluid is probably only partially secreted by Brunner's glands and since the secretin injected was not chemically pure, he suggests that it may have contained enterocrinin.

Intestinal Juice.—Numerous attempts have been made to obtain information as to the mechanism of secretion of intestinal juice. A detailed account of the experimental methods employed and the results obtained up to 1928 is given by Babkin.[6]

Decrease in enzyme production by the jejunum has been observed during fasting; feeding, however, produced a decrease followed by a rise. Ileal loops responded to feeding in a similar manner but fasting did not decrease enzyme production.[72]

Evidence has been obtained that mechanical stimulation elicits an immediate flow of intestinal juice. The quality of the secretion, however, depends on the character of the mechanical stimulus employed. It has been suggested that this secretion is due to a reflex involving only the neurones of the enteric plexuses. Many chemical irritants have been found effective. Electrical stimulation also causes some secretion.

Recent experiments show that the secretion of intestinal juice is influenced by secretagogs and/or hormones, as the digestion of food is accompanied by secretion of a larger volume of juice as well as a greater enzyme production in a transplanted denervated loop of the small intestine. Some foods appear to have a greater stimulating effect than others, but further evidence is required to demonstrate the presence of specific effects of food on intestinal secretion.

The experiments of Sawitsch and Soshestwensky[71] are frequently cited as evidence that vagal impulses influence the secretion of intestinal juice. These observers note that vagus stimulation caused an increase in both the liquid and the enzyme secretion of the intestinal juice. Within certain limits, the enzyme content of the intestinal secretion increased with increasing strength of stimulation. Atropine abolished the effect.

There is, however, not enough evidence to justify one to say definitely what influence the vagus has on the secretion of the small intestine.

The hypothesis has been advanced that the central nervous system exhibits a tonic inhibitory action on the intestinal glands. The evidence for this view is briefly as follows: Section of all the preganglionic sympathetic fibers was followed by secretion from all the small intestine. Within a few days after the operation the secretion ceased. The ganglion cells of the solar plexus are stated to take on the power of inhibiting secretion: this "paralytic secretion" was inhibited by atropine.[89]

Nassett, Pierce and Murlin[64] have discussed the manner of release from nerve inhibition in the normal innervated loop of jejunum. They pointed out that the combination of the presence of the catheter as the local stimulus with the humoral effect of a meal is insufficient in some animals to overcome the nerve inhibition and cause an increase in secretion. After complete denervation, the same combination of stimuli produces copious secretion in the same dogs. They therefore suggested that the local stimulus may be the presence of food itself, *i. e.*, a local mechanical and chemical stimulus on the particular portion of the intestine concerned. In some dogs the local stimulus afforded by the catheter was sufficient, and the response to a meal was essentially unaltered by complete denervation of the loop.

Nassett, Pierce and Murlin concluded, as a result of animal experiments, that there are at least three components in the control of secretion from transplanted loops: (*a*) local mechanical stimuli, (*b*) inhibitory impulses by some of the extrinsic nerves and (*c*) humoral stimulation by digestion of food in another part of the gut.

Secretin when injected stimulates secretion of juice in a denervated loop of bowel. Ågren[1] has shown that secretin also causes a flow of intestinal juice in man. Recently a hormonal mechanism (enterocrinin) for the stimulation of intestinal juice has been demonstrated. The hormone which has been obtained from the small and the large intestine is distinct from secretin. It augments the secretion of enzymes as well as fluid (Nassett[18]). Nassett is of the opinion that the hormone is not secretin and that the secretin used by Agren may have contained "enterocrinin."

Owles[66] found that in man local mechanical stimuli and oral administration of water, dextrose, eggs, milk and iron salts increase the volume and enzyme output of intestinal juice. The secretion of juice in response to a given stimulus is greater at higher than at lower levels of the small intestine.

From the evidence available, it appears that the secretion of intestinal juice is controlled by the following factors: (1) mechanical stimuli, (2) secretagogs and (3) hormones. The secretion may also be influenced by the action of the extrinsic nerves.

Secretion of Bile and Evacuation of the Gallbladder.—It is not proposed to discuss the factors influencing the secretion of bile and the evacuation of the gall-bladder here, as the subject is dealt with by Professor Ivy in another section of this book.

Colonic Juice.—The mucus producing cells (goblet cells) may be directly stimulated by irritants to produce their secretion. The irritant appears to act on some secretory mechanism which requires oxygen.[25]

Wright and Florey[87,88] have recently reported the effects of stimulation of parasympathetic and sympathetic nerves on the secretory activity of the colon. Stimulation of the N. erigentes caused secretion. Stimulation of the hypogastric nerves had no effect, but when the N. erigentes and the hypogastric nerves were stimulated together the augmentor effect of the N. ergentes was inhibited. The response to stimulation of the parasympathetic nerves was enhanced by eserine and abolished by atropine. Acetyl choline and pilocarpine stimulated secretion. The only enzyme detected in the secretion was dipeptidase. According to Lium and Porter[51] the secretion of mucus is not influenced by digestion or starvation. Dehydration was shown to decrease secretion but any factor which increased the muscular activity of the explant increased secretion.

Examination of the factors influencing secretion lead to interesting speculations as to the possible causes of conditions such as "mucous colitis."

Absorption.—The products of digestion in the small intestine are absorbed by the surface epithelium of the intestine. The epithelial cells which cover the villi acts as a membrane, which is normally completely permeable to water and crystalloids in both directions and impermeable to colloids. The entrance of water-soluble substances into the mucosa is explained mainly by diffusion, and the movement of water out of and into the intestine by osmosis. Further hydrostatic pressure within the intestine created by the intestinal movements tends to drive water and dissolved substances across the epithelial border (see Best and Taylor[12]). Some observers state that water-soluble substances are absorbed through the intercellular cement substances.

In considering the process of absorption it must be remembered that the membrane is built up of living cells, so that changes in the circulation and other factors can influence its state. Solubility in lipids, surface activity and chemical changes modify the simple diffusion process through the membrane.

For diffusion, the substances in the intestine must be in aqueous form. In the process of making the substances diffusible, hydrotrophy is important. Verzar and McDougall[82] define hydrotrophy as "the property of some asymmetric, strongly surface-active water-soluble organic compounds to disintegrate water-soluble substances to molecular complexes in which the hydrotropic molecules surround the insoluble molecule and render it soluble and diffusible."

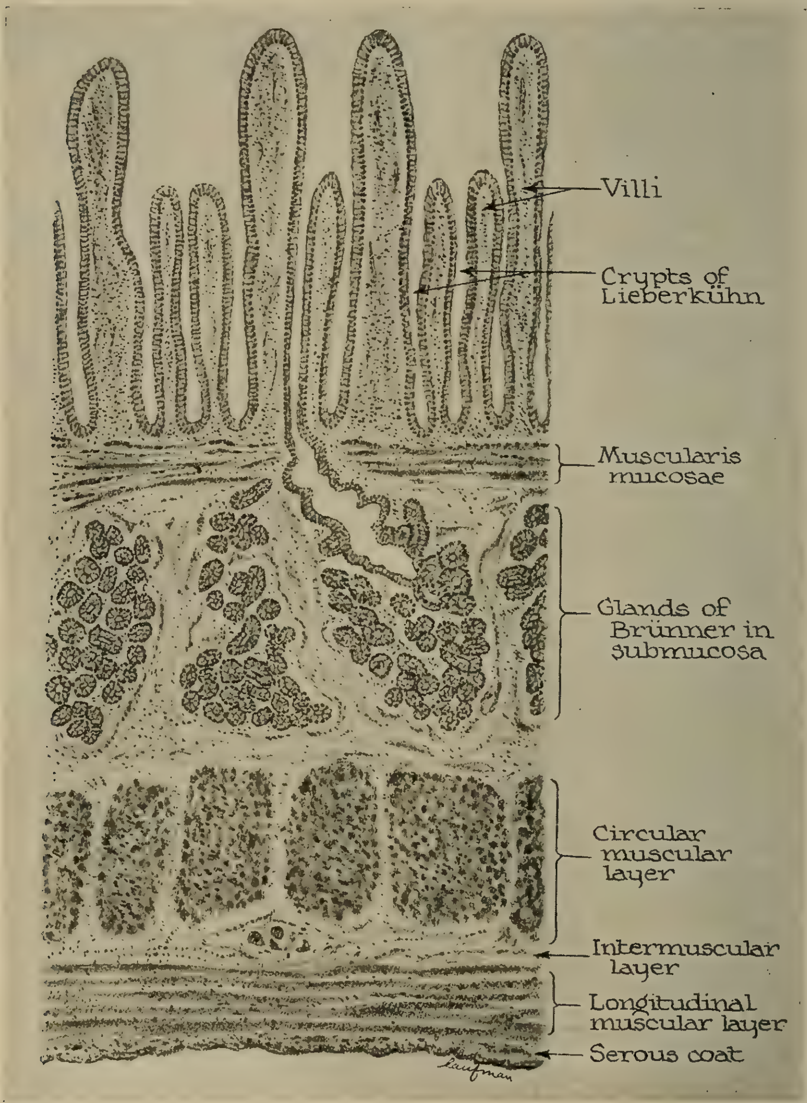

Fig. 96.—Section of duodenum of cat, showing Brunner's glands. (Reproduced with the permission of H. M. Carleton, from *Essentials of Histology*, by E. Sharpey-Schafer and H. M. Carleton, Longmans, Green & Co.)

A special selective absorption can be demonstrated for certain substances. It has been shown that galactose and dextrose are absorbed at about three to four times the rate of most of the other sugars. This selective effect is stated to be due to an active chemical process (phosphorylation). The process is briefly as follows: Galactose and dextrose are combined with phosphoric acid to form hexose phosphates in the cells of the mucosa. The accelerating action of the phosphorylation is due not to increased diffusibility of the hexose phosphate but probably to the effective removal of free hexose from the epithelial cells. The hexose phosphate is apparently broken down again before entering the blood stream. Through the constant transformation of the diffusing substances in the cells, the diffusion gradient is kept high, and the synthesis finally acts by increasing the diffusion process and hence the velocity of absorption.

If the process was one of pure diffusion, the absorption would depend on the concentration of the solution and molecular size. It is true that a greater amount of mannose and of xylose are absorbed when the concentration of the solution is increased, but with galactose and dextrose the amount absorbed in a given time is the same for almost any concentration. According to Shay *et al.*[74] this may be attributed in part at least to retardation of gastric emptying and the dilution mechanism of the duodenum. Further evidence for a special process is provided by the fact that phosphorylation and therefore the elective absorption of monosaccharides are inhibited by monoidoacetic acid.

The manner in which fat is absorbed from the small intestine is still a matter of controversy. Fat hydrolysis is undoubtedly important, but evidence has been put forward that in some animals, at least, fat can be absorbed in the form of fine particles. Readers particularly interested in this aspect of the subject are recommended to refer to the reviews by Bloor[13] and Frazer.[30]

Now glycerol is water soluble, but fatty acids are practically insoluble. The explanation that fatty acids form soluble soaps is untenable, in view of the fact that the *p*H of the contents of the intestine is probably never greater than 7. The absorption process appears to depend first on the hydrotropic action of the bile acids. Glycocholic and taurocholic acid with the fatty acids form hydrotropic compounds which are stable and diffusible at the *p*H which exists in the intestine. It is probable that the bile acid—fatty acid complex is broken down as soon as it enters the epithelial cell. The bile acids are then absorbed at the surface of the epithelial cell, and they form there the water-soluble and diffusible complexes which bring the fatty acids into the cells.

Phosphorylation also appears to play an important role in fat absorption. The hypothesis is put forward that phospholipids are synthesized in the intestinal mucosa and then distributed to the body through the blood stream. Sinclair and Smith[77] postulate that in the process of synthesis of the phospholipids there is a selection of one molecule of a saturated fatty acid for each molecule of an unsaturated acid.

Frazer[27,28,29] has suggested that the ultra microscopic particles visible in blood under dark-ground illumination are particles of fat with a layer of globulin adsorbed on the surface. He claims that particle counts provide a simple and rapid method of comparatively determining the fat content of blood. He has shown that when rats are fed with olive oil the particle count in the systemic circulation rises, whereas the particle count in the portal blood decreases. When a mixture of glycerol and fatty acids is fed, however, the situation is reversed, the particle count in the systemic circulation falls and in the portal blood rises. It was also shown that when rats were fed on fats stained with Sudan III, the fat depots become stained with dye, but not the liver; on the other hand when stained fatty acids and glycerol were fed, the liver showed signs of the stain and the depot fat did not. Frazer concludes from this that that portion of the dietary fat which is hydrolyzed forms soluble complexes with bile salts and is absorbed into the portal circulation to be stored by the liver; the remainder of the dietary fat is absorbed without hydrolysis into the lymphatic system and is discharged into the general circulation to be stored in the fat depots.

The amino acids (the end product of protein digestion) are normally absorbed by the time the chyme reaches the end of the small intestine. It has been suggested that amino acids are selectively absorbed, since their absorption rates are greater than would be anticipated on the basis of their molecular volumes. As a result of their investigation of the absorption of polyhydric alcohols, aliphatic amines, and fat soluble compounds, Höber and Höber[41] conclude that molecular volume, fat solubility, and chemical affinities for the mucosal cell membranes are factors which regulate the rate of absorption of those substances which are not selectively absorbed.

It has been stated that water-soluble substances are absorbed mainly by diffusion through the intercellular substance of the intestinal epithelium. Evidence has been put forward, however, that even absorption of sodium chloride may require active intervention on the part of the cells.[22]

Nearly all calcium, whether in milk, vegetable or salts, seems to be utilizable, even when insoluble (Shohl[76]). Increased acidity of the small intestine is stated to favor absorption, while increased alkalinity gives rise to the formation of insoluble salts and less absorption takes place. When phosphate intake is excessively high, insoluble tribasic calcium phosphate is formed, and calcium absorption is decreased.

Phosphorus is absorbed in the form of inorganic phosphate. Vitamin D is necessary for calcium and phosphorus absorption. Phytates which are present in many cereals decrease the absorption of calcium and magnesium but not potassium; about 50 per cent of the phosphorus of sodium phytate is absorbed.[53]

It is now known that inorganic iron in any soluble form may be absorbed and utilized by the body. The truly organic iron, namely, that combined *in heme*, is not available, since it is not broken down in the digestive tract. The inorganic iron of the food, which is in the form of ferric iron, is reduced to ferrous iron, in which form it is mainly absorbed. It has been noted that the intestinal mucosa has a high content of glutathione, which may reduce ferric to ferrous iron.

McCance and Widdowson[52] have shown in man that the elimination of iron occurs very slowly. The recent work of Hahn and his colleagues[36] suggests that the absorption of iron from the gastro-intestinal tract is regulated according to the size of the iron reserves of the body. The view is put forward that absorption is governed by the plasma iron concentration acting through a mucosal acceptor.

The evidence with regard to excretion by the colon is conflicting. Contrary to former views, recent work has shown that only lead and radium and possibly mercury are excreted through the large intestine and that none of the ordinary di-valent ions are excreted by either the small or the large intestine.

The study of a human subject after low ileostomy has shown that the organic constituents of the food are digested and absorbed before they reach the colon. The contents of the ileum delivered to the colon seem to be nearly in osmotic equilibrium with the blood. The ileal material contains, however, a larger amount of sodium and chloride than the feces.

The human colon appears to have no specific function in the excretion of metals, as no substantial amount of calcium and iron were recovered from the isolated colon (Welch, Wakefield and Adams.[86] Water is absorbed in the large intestine, as the feces contain about one-third of the water which enters the large intestine.

The normal adult feces have a water content of 65 to 80 per cent. Of the dry matter, one-third is bacteria, and the rest consists of the remains of intestinal secretions, substances excreted by the intestine, cellular debris and small amounts of food residue.

Thorpe[80] gives the following figures for the composition of dry feces: nitrogen, 5 to 10 per cent; "fat," 10 to 20 per cent, and ash, 10 to 20 per cent.

The normal color of feces is brown, owing to the presence of stercobilin and urobilin; it varies, however, with the diet. The odor is due mainly to indole and skatole; mercaptan and hydrogen sulfide may contribute. The average $p\text{H}$ is 7 to 7.5.

The fat of the feces can be divided into split and unsplit fat. The neutral fat is derived from bacteria and the breakdown of epithelial cells. The split fat is diminished on a low fat diet and therefore appears to represent in part unabsorbed fatty acids. The percentage of nitrogen in the feces is little altered by the amount of protein ingested. The most abundant salts are calcium and phosphate.

Movements in Man.—Direct observation by means of barium meals and and *x*-rays is now used as the routine method of studying the movements of the small and the large intestine. The following description is based on the account given by Barclay:[7] for a fuller account readers should consult monographs on the subject.

In the first part of the duodenum the food forms a definite shadow known as the duodenal cap or bulb. Its shape is often unchanged for a long period; when the food appears to be pushed on by a general contraction into the second part of the duodenum.

Beyond the first part of the duodenum fragmentation occurs. The sharp, well defined shadow of the first part of the duodenum is followed by an ill defined and much diffused outline. In many instances, however, the food passes on from the first part of the duodenum in large quantities and therefore gives a fairly good shadow of the second and third parts of the duodenum.

Four movements have been described as occurring in the duodenum: (1) contraction of the cap, (2) peristaltic contraction of the duodenum (other than the cap) propelling food forward, (3) contraction of the duodenum (other than the cap) forcing the contents backwards and (4) segmentation or mixing movements.

From the duodenojejunal flexure onward it appears impossible to make accurate observations, for the fragments are so fine that they do not form a definite shadow on the screen.

Barclay[7] suggested that the muscularis mucosæ is capable of dealing with the propulsion, fragmentation and turning over of the intestinal contents effectively under easy conditions. When the intestine owing to rapid emptying of the stomach, becomes over-loaded, peristaltic waves occur, which push the food onward but seem to involve only a small section of gut before they die away, to be followed by other waves in the same section driving the contents in the reverse direction. According to Barclay, peristalsis is much less important than the constant motion of the muscularis mucosæ.

Peristalsis and segmentation, which give rise to fragmentation of food, are marked in the jejunum.

In the ileum definite shadows of opaque food are formed and remain more or less inert. Waves of persitalsis are seldom seen. After a delay, the food appears to pass into the cecum by a segmenting constriction of the terminal part of the ileum. Opaque food is seen at the ileocecal valve fifteen minutes to two hours after the taking of the meal. Food does not appear in the cecum for one and one-half to two hours.

The food collects in the cecum and ascending colon, forming a well defined shadow, which has usually a segmental appearance due to the sacculations of the wall. "Mass" movement, first described by Holtzknecht[42] and later confirmed by Hurst,[43] appears to account for the progress of food for considerable distances along the bowel.

The movement usually starts in the region of the hepatic flexure. The outline of the transverse colon becomes smooth like that of a ribbon, with parallel borders. Then the ribbon breaks at the hepatic flexure, and the food is forced forward into the descending colon, which had been empty. The passage from one portion of the colon to the next is extremely rapid. The movement occupies at the most three seconds. Immediately after the transference is accomplished, the haustral segmentation reappears. These movements are stated to occur three or four times a day after entrance of food into the stomach ("the gastrocolic reflex"). It should be pointed out that these movements are seldom seen during a radiological examination.

In man, the rectum is normally empty, and fecal matter accumulates proximal to the pelvirectal flexure. As a result of one of the driving movements, fecal matter enters the rectum, and a desire to defecate is created.

In the act of defecation, strong "peristaltic" contractions occur throughout the cecum and colon accompanied by shortening of the longitudinal fibers which are disposed in three bands of the anterior, inner and posterior aspects of the intestine; the intra-abdominal pressure is raised by contraction of the diaphragm and of the abdominal muscle,, and the feces are forced through the relaxed sphincters of the anal canal. The levator ani aids defecation by pulling the anal canal craniad over the extruding fecal mass, and the puborectal fibers of the levator ani, by constricting the rectum, clear out the last traces of fecal matter. Fecal matter is removed normally only from the distal part of the gut (Garry[32]). The mechanism of defecation, provided delivery of fecal material from the colon is adequate, depends primarily upon the reaction of the rectum to distension.

It is suggested by Denny-Brown and Graeme-Robertson[21] that the pelvic colon possesses the same motor function as the rectum. It appears possible that the most distal pelvic colon and the rectum serve together as an evacuating mechanism which when filled in sufficient degree from above, contracts powerfully upon its contents and expresses them through the sphincter ani. If the external sphincter obstructs the passage the same contraction drives the greater bulk to the reservoir of the colon. Alvarez and Freedlander[3] have shown that the rate of progress of residues through the bowel varies markedly in normal persons. They gave to each subject a capsule containing fifty tiny glass beads and counted the number of these beads passed with feces each day. Two subjects passed 85 per cent in twenty-four hours. Most of the subjects examined took four days to get rid of 75 per cent of the beads. A third group took nine days to pass 50 to 60 per cent. These investigators have observed also that the fractions of a barium meal passed in successive days vary in the same way.

Recently Wallace and his associates[84] have demonstrated that 10 per cent of the subjects examined evacuated barium in twenty-four hours; two-thirds required three days, and the remainder did not completely expel the barium meal until the fourth or fifth day.

Ileocolic Sphincter.—The ileocolic sphincter has been examined in patients with cecal fistula. The sphincter appears as a papilla 1.8 centimeters in diameter and projecting 1 centimeter from the wall of the cecum. From time to time rhythmic changes in height and width of the papilla were observed, which were associated with to and fro contractions of the terminal part of the ileum. With each enlargement, a small amount of semifluid chyme, about 4 cubic centimeters entered the cecum. Under the influence of excitement relaxation occurred every one or two seconds. Normally the sphincter is contracted tightly, and it is interesting to note that attempts to distend the sphincter are accompanied by pain (Rutherfore[70]).

It has been pointed out that the blockage of the waves at the sphincter may be due in part to differences in the muscle above and below the sphincter and even to peculiarities of the sphincter itself. The muscle of the colon appears to be more sluggish than that of the ileum, and its rhythmic activities are different. The muscle of the sphincter can contract and prevent reverse waves in the colon, which drive the cecal contents into the ileum. Cannon[16] found, however, that if an enema is held in the colon long enough, some of it will run back into the cecum.

The rate of passage of the ileal contents into the colon is increased when food is taken.

Movements in Animals.—In order to obtain information on the movements occurring in the small intestine, numerous investigators have been made on animals. Four types of movements are described: (1) rhythmic, segmenting movements; (2) swaying, or pendulum, movements; (3) movements of the intestinal villi, and (4) peristalsis.

Rhythmic, Segmenting Movements.—These movements are due to localized rhythmic contractions of the circular muscle generally in the duodenum and jejunum. According to Cannon[15] constrictions occur at regular intervals along the length of the gut and divide the food into small ovoid pieces. A moment later each of these segments is divided into two halves, and immediately after the division neighboring halves rush together and merge to form new segments. The next moment these new segments are divided, and neighboring halves unite to make a third series, and so on.

These kneading movements mix the foodstuffs thoroughly with the digestive juices. They also aid absorption by spreading the chyme over the mucosal wall. Segmenting movements have been observed in the human being at the rate of eight per minute. Krishnan[48] stated that when the circular muscle contracts in a segment of bowel the longitudinal muscle relaxes, and *vice versa*.

Pendulum Movements.—In the rabbit and to a certain extent in other animals, as well as in man, a local mixing of the intestinal contents is brought about by pendulum movements. These movements, like the segmenting movements, are simply annular constrictions. During the movements the contents of a short loop are thrown from one end to other. They have, however, no direct effect on the movement of food, but exert a purely local, churning action. The circular and longitudinal muscles usually contract together at a frequency of from twenty per minute in the duodenum to about ten per minute in the lower part of the ileum (Alvarez[2]). According to Krishnan,[48] the pendulum movements are phenomena of the longitudinal muscle, with a reciprocal inhibitory effect on the circular muscle.

Movements of the Intestinal Villi.—Two or three hours after feeding, according to Verzar and McDougall,[82] the villi of a dog's intestine show rhythmic contractions at a rate of about six per minute. Not all the villi move at once; some remain quiet for long periods while their neighbors are steadily contracting and relaxing. The movements of each villi seem to be independent of those of its neighbors. The villi shorten quickly and lengthen more slowly.

A second type of movement of the villi, usually termed the pendulum movement, is also seen. This movement consists of a swaying of the villi, to and fro, without shortening.

A third type of movement is a tonic contraction, when the villi contract sharply and remain contracted for a long period. This type of movement is probably not physiologic, as it only occurs after abnormally strong chemical stimuli.

On contraction the villi become shorter but not thicker, and it has been concluded that the contents of the central lacteal are pressed out at each contraction.

It seems that the villi have to be swollen before they contract. The shortening of the villi is stated to be due to contraction of the plain muscle fibers.

Rhythmic movements of the villi continue in an isolated piece of intestine. Stimulation of the vagi augments movements; stimulation of the splanchnic nerves decreases activity (Kokas and Ludány[47]). Pressure stimuli elicit a reflex response, and it is suggested that the reflex center is present in Meissner's plexus.

According to Kokas and Ludány,[45] the movements are set up by a hormone "villikinine," set free in the duodenum by the acid chyme. It is present in the intestinal mucosa in the form of a pro-substance (Kokas and Ludány[46]).

The absorption of substances which diffuse directly into the blood capillaries is not much influenced by contractions of the villi, while the absorption of substances such as fat, which fill the central lacteal with an emulsion of droplets, is accelerated.

Peristalsis.—In 1899 Bayliss and Starling,[8] as a result of observations on animals, described a phenomenon which they called "the law of the intestine," which can be produced by mechanical stimulation such as that which the presence of food would afford. The nature of this movement was demonstrated in the intestine *in situ* but separated from any connections with the central nervous system. It can also be obtained in the excised gut. A gentle pinch at any point causes a cessation of the rhythmic contractions in front of the place excited, together with a diminution of the state of moderate tonic contraction in which the intestinal muscle normally exists and on which the rhythmic contractions are superposed.

Coincidently with this relaxation there is an increased tonic contraction, with greater vigor of rhythmic movements above or behind the place excited.

As this phenomenon depends on the existence of the enteric plexuses, Cannon[17] suggested the name "mesenteric reflex." It is questionable, however, whether relaxation of the bowel always occurs in front of the stimulated point. A number of investigators have failed to observe the reciprocal effect, a simple contraction above and below being the only movement obtained on stimulation of the bowel. Krishnan[48] stated that in peristalsis a wave of longitudinal muscle contraction with the circular muscle relaxed precedes a wave of circular muscle contraction with the longitudinal muscle relaxed. The "law" of Bayliss and Starling is applicable only to the action of the circular muscle layer.

According to Cannon[15] the phenomena of peristalsis and segmentation are usually combined in some manner while the food passes through the small intestine. Peristalsis is observed normally in two forms: as a slow advancing of the food for a short distance in a coil and as a rapid movement sweeping the food without pause through several turns of the gut. The latter form is frequently seen when the food is carried on from the duodenum, and it may readily be produced in other parts of the small intestine by an enema of soapsuds.

When a mass of food has been subjected for some time to the segmenting activity of the intestine, the separate segments, instead of being again divided, may suddenly begin to move slowly along the loop in which they lie. That this movement is not a swinging of the coil as a whole but a peristaltic advance of separate rings of its circular musculature is made probable by the fact that the succeeding segments follow along the same path their predecessors have taken. The advance of the little pieces may continue for 7 or 8 centimeters, when finally the front piece stops or meets other food. Then all the succeeding pieces are swept one by one into the accumulating mass, which at last lies stretched along the intestine, a solid string manifesting no sign of commotion.

Another form of slow peristalsis is frequently observed when the food is pushed forward, not in small divisions, but as a large lump.

Peristaltic Rushes.—Most of the forwarding of the intestinal contents, according to Alvarez and Mahoney,[4] is brought about by large waves which from time to time run down the bowel. These waves may arise in any part of the small bowel and may run short or long distances. In an animal suffering from diarrhea the waves have been observed to run from the pharynx to the anus.

The majority of waves in the duodenum appear about the time that a gastric wave reaches the pylorus. The waves in the duodenum are, however, not necessarily correlated with the arrival of the gastric contents in the duodenum, as the duodenal tonus contractions, from which they seem to originate, appear a few seconds before the gastric waves reach the pylorus. Many of the rushes seem to begin in swallowing movements, but others can be initiated by stimulating the duodenum.

At the commencement of the movement, a loop fills from above. The tone of the loop rises; the amplitude of the rhythmic contractions increases, and the material is thrown backward and forward more and more forcibly by the two ends of the loop. Usually a number of loops are active at the same time. The food, as a result of a series of waves, finally reaches the ileocolic sphincter. When the waves start they travel at from 2 to 4 centimeters a second, but in the ileum the rate is much faster, 7 to 25 centimeters a second.

Alvarez[2] pointed out that not only will a rush wave go on down the bowel after it has left the burden of its contents behind, but it may pick up some food farther down. Even when the bowel is cut in two and the ends tied over a short piece of glass tubing, the waves go on down the bowel. Peristaltic rushes also occur when the segment of bowel ahead is powerfully contracted. Alvarez[2] suggested that the contraction is an effort on the part of the bowel to stop the rushes.

Collating the evidence it may be concluded that the onward movement of food is not necessarily dependent on the presence of inhibition in front of the bolus, and that the movement frequently used to propel the food forward is the peristaltic rush. According to Alvarez[2] stimulation of the bowel at any point leads to the holding back of material coming down from above and the hurrying onward of material already below.

Carey[19] described the circular and longitudinal layers as close spiral and long spiral, respectively. These layers run in a counter-clockwise direction from above downward. The continuous close spiral musculature is considered to be responsible for the localized wave of contraction occurring during the propulsion of food material along the small intestine. The long spiral fibers are responsible for the dilatation that precedes the contraction down the intestine. The recent observations of Franklin and Maher-Loughnan[26] supported Carey's view that there is a close spiral arrangement of muscular fibers in the small intestine of certain species. Gunn and Underhill[35] suggested that the muscularis mucosæ of the cat's intestine consists of fibers which run not in a directly circular or longitudinal direction, but obliquely or spirally.

Reid, Ivy and Quigley[69] have observed that a bolus inserted into the proximal end of a Thiry-vella fistula of the jejunum of a dog rotated 360 degrees in passing through 25 to 35 centimeters of intestine. The direction of rotation was counter-clockwise from above downward.

Antiperistalsis.—Antiperistalsis, or reverse peristalsis, occurs as a normal mechanism in the duodenum and ileum. It is probable that the duodenal contents flow backward during the interval when the pressure is lower in the pars pylorica than in the cap. Regurgitation in the duodenum can be observed fluoroscopically, but regurgitation from the cap into the stomach cannot be seen. It is interesting to note that the regurgitation of duodenal contents is supposed to be more marked when fats are eaten. Fats decrease the tone and inhibit the movements of the stomach and increase, it is stated, the tone and activity of the duodenum, a reaction which would reverse the normal gradient of pressure between the two organs.

Bolton and Goodhart,[14] among others, regard duodenal regurgitation as a normal mechanism for regulating the curve of gastric acidity.

Martin[59] in a recent article discussed the evidence. He concluded that although the concentration of hydrochloric acid may be reduced by duodenal regurgitation, that relation is secondary and the primary cause is a decreased secretion in volume of acid, with an increased secretion of neutral chlorides.

Alvarez's Theory of Gradients.—Alvarez[2] suggested that the nerves do not ordinarily expedite conduction and that the peristaltic or wave-like movements can take place along gradients without the help of specially designed nervous mechanisms.

A gradient is a graduation, usually in some attribute or state or force or activity, which is to be found between certain limits in space or time. It is an expression of relationship. Thus, to use Alvarez's simile, the gradient of a railroad is the degree of inclination of the track as it spreads mile by mile over its territory; it can be represented by a graph in which heights above sea level are plotted as ordinates and distances from some starting point as abscissæ. The basic gradient, therefore, makes it easier for waves to trend in one direction than the other. Some tubular organs may be likened to ponds which are level to begin with, while others are more like rivers which have definitely established gradients. In the first case, waves spread equally well in all directions; in the second, the waves spread more easily downstream than up.

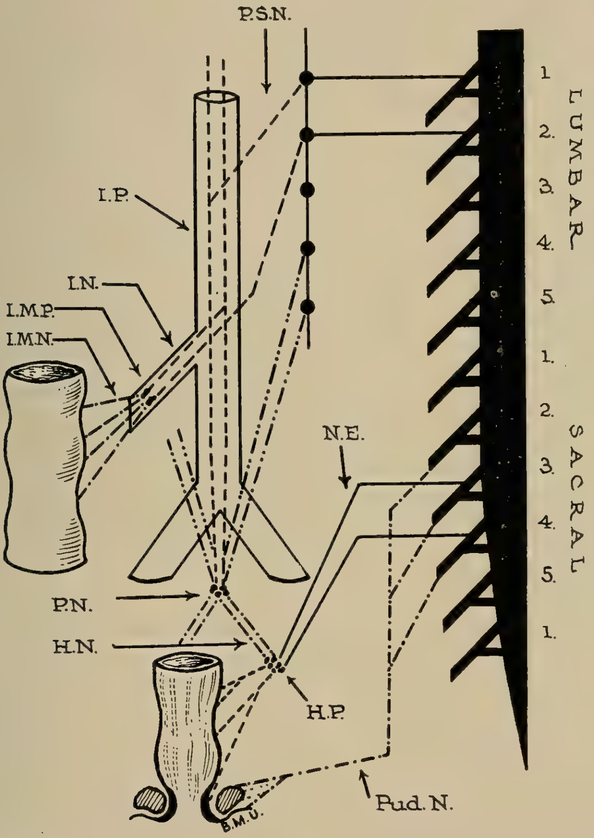

FIG. 97.—Nerve outflow to the distal part of the colon in man (redrawn from Garry[25]). *P.S.N.* indicates pelvic splanchnic nerves; *I.M.P.*, inferior mesenteric plexus; *I.M.N.*, inferior mesenteric nerves; *P.N.*, presacral nerve; *H.N.*, hypogastric nerve; *H.P.*, hypogastric plexus; *Pud.N.*, pudental nerve; *I.N.*, intermesenteric nerve; *I.P.*, intermesenteric plexus; *N.E.*, nervi erigentes.

A rhythmic gradient exists in the bowel from the pylorus to the colon. Normally the duodenum beats seventeen times per minute and the ileum ten times per minute. Warming a strip of ileum speeds up its metabolism; its rate of contraction is raised to seventeen times a minute; the latent period is shortened and the form of contraction curve altered. Rhythmicity, tone, irritability, latent period and force of contraction are graded from above down, being higher in the duodenum than in the ileum. Further, the oxygen consumption, carbon dioxide production and catalase content of the muscle are decreased from the duodenum to the ileum. These differences are spoken of as "physiologic gradients." The direction and swiftness of the peristaltic rush is supposed to depend on the differences in the intestines of the physiologic gradient at any two levels of the digestive tube.

Nervous Control.—Magoun[58] emphasizes that the full role of the autonomic nervous system in the integration of bodily processes is only exerted through the action of essential supranuclear centers in the medulla, hypothalamus and cerebral cortex. It should be pointed out, however, that the viscera, though dependent on the nervous system for the integration of reactions and necessary adjustments, are capable of independent function after section of the extrinsic nerves.

The visceral nervous system include the representations of the sympathetic and parasympathetic systems in the cerebral cortex, hypothalamus, medulla and spinal cord together with the Way In and Way Out.

Centers.—Fulton[31] recalls that Bochefontaine as early as 1876 observed that electric stimulation of the dog's sigmoid gyrus caused contraction of the stomach, especially near the pylorus, but that the pyloric sphincter itself was relaxed and that there was usually an increase in the peristaltic movements of the small intestine and colon. These observations were confirmed by Hlasko[40] and Bechterew.[10]

Since that time numerous investigations have been made to demonstrate that electrical stimulation influences the activity of the gastro-intestinal tract (see Annual Reviews of Physiology). Evidence has also been obtained that frontal lobe lesions cause some disturbances of motility and probably also of secretion.

Wang *et al.*[85] state that stimulation of the hypothalamus anterior to the infundibulum was observed to produce immediate blanching and occasional inhibition of motility of the intestine followed by an excitatory phase lasting for several minutes and unaffected by section of both vagi. Vagal effects were noted after stimulation of the region behind the infundibulum. Studies on the brain of the cat by Sheehan[75] also indicate that inhibition of peristalsis in the stomach, intestines and particularly the colon can be produced by adequate stimulation of the lateral hypothalamic area. Motor responses of the gastro-intestinal tract to proper hypothalamic stimulation were less definite.

The function of "autonomic" centers in the mid-brain and medulla has been examined by a number of investigators, and attempts have also been made to trace descending pathways.

Way In.—Using dilatation of the pupil as an index (see McDowall,[54]) it has been possible to trace out the pathways of afferent fibers which innervate abdominal viscera.

The duodenum is supplied by afferent fibers of the vagus and the splanchnic nerves, but the jejunum and ileum are innervated mainly if not solely by the splanchnic afferent fibers.

McSwiney and Suffolk[56] have shown that the attachments to the spinal cord of the splanchnic afferent fibers which supply the small intestine are as given below:

Area	*Upper Limit*	*Lower Limit*
Duodenum	T6	L1
Jejunum	T7	T12-T13

More recently it has been possible to demonstrate that afferent fibers to the ileo-colic sphincter enter the spinal cord in the dorsal roots from T7 to L2.[57] According to Un Kauf[81] the afferent fibers to the large intestine also enter the spinal cord in the dorsal roots from T7 to L2. In their course these fibers pass through the upper four lumbar ganglia to the sympathetic chains. The afferent fibers of the vagus nerves do not conduct impulses from the ileo-colic sphincter or the large intestine.

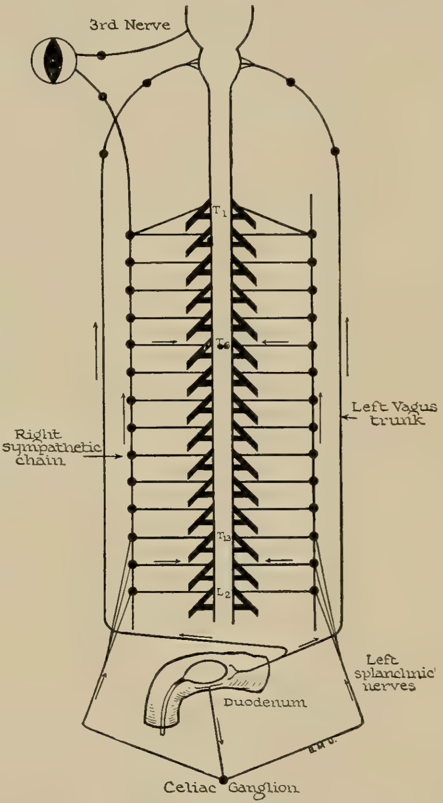

FIG. 98.—Diagram to illustrate the visceral afferent fibers in the vagi and the splanchnic nerves. The spinal vagus fibers are not shown in the diagram.

Way Out.—*Small Intestine.*—The small intestine is innervated by fibers of the parasympathetic and sympathetic divisions of the autonomic nervous system. The cell station of the sympathetic excitor neurone is in the cœliac plexus, while that of the parasympathetic neurone is in the enteric plexus.

Stimulation of the vagus nerve results usually in increase of the tone and augmentation of movements, whereas stimulation of the splanchnic nerves causes a decrease of tone and inhibition of movements. In some instances reverse effects may be obtained. It is possible that the dual effects observed on stimulation of the vagus or sympathetic nerves might be explicable on the basis that each of these nerves contains cholinergic and adrenergic nerves (Harrison and McSwiney[39]).

The effects of division of these fibers reported in the literature are in the main the results of acute experiments. It is stated that section of the vagi and splanchnic nerves causes a temporary hypotonicity and a diminution in peristalsis, but after a short period little difference from the normal can be observed.

Large Intestine.—It is uncertain what part the central nervous system plays in co-ordinating the various movements of the large bowel.

Stimulation of the sympathetic nerves (thoraco-lumbar outflow) causes contraction and/or inhibition of the colon. Contraction of the ileocolic and internal anal sphincter is generally obtained.

Stimulation of the pelvic nerves (bulbo-sacral outflow) usually causes contraction, but transient relaxation frequently occurs. The effect on the internal anal sphincter varies in different animals. It is probable that the sympathetic and parasympathetic outflow both contain adrenergic and cholinergic fibers.

Reflexes.—Little is known of the reflex mechanisms influencing the secretions and motility of the small and large intestine with the exception of the act of defecation. It is stated that the entry of food into the stomach causes a great increase in the rate of passage of the ileal contents into the colon (gastro-ileac or gastrocolic reflex). A receptive relaxation of the colon has also been described.

Viscero-somatic and somatic-visceral reflexes have been demonstrated. It is possible to show, for example, that stimulation of the intestine may cause flexion, extension or alternating movements of the hind limbs. Again, stimulation of a somatic afferent nerve may cause inhibition of intestinal movement.

Denny-Brown and Graeme-Robertson[21] have obtained valuable information of the nervous control of defecation. Automatic defecation resulting from destructive lesions of the sacral innervation of the rectum and anus in man has been studied. In these conditions, contraction of the rectum with reciprocal relaxation of the anal sphincter has been recorded.

The reciprocal relation between the rectum and the involuntary sphincter is nervous in mechanism and the adequate stimulus is tension on the wall of the rectum. Passive tension brings about a slight relaxation of the sphincter; active tension, however, is a more powerful stimulus.

The sympathetic nerves (hypogastric) to the rectum and anus are not essential. Indeed the nervous mechanisms for these reflex reactions appear to reside in the peripheral nerve plexus. At the same time, reflex activity of the sacral segments of the spinal cord beings about a more massive and complete response.

The postural tone of the rectum and the sphincter ani is related to the passive tension of the muscles. A rapidly increasing tension causes tonic contraction to give way to phasic contraction. The postural tone is dependent on the peripheral nervous mechanism.

It has been demonstrated that following a transverse lesion of the spinal cord or cauda equina, fully developed defecation can secure efficient evacuation of fluids and that this reaction can be elicited from the rectum alone. The defective evacuation of solids resulting from these nerve lesions appears to result not from deficient reaction to distention of the rectum but from lack of sufficient propulsive power in the act.

The statements that section of the thoraco-lumbar outflow leads to increased activity of the colon and that after section of the pelvic nerves the movements become weak and sluggish must be received with caution, even though patients suffering from certain types of constipation (Wade and Royle[83]) are reported to have benefited by section of the sympathetic outflow.

Sphincters.—Little is known about the effects of destruction of the lumbosacral part of the cord on the ileocolic and internal anal sphincter. Denny-Brown and Graeme-Robertson[21] report that voluntary control over defecation extends directly only to the external voluntary sphincter ani. The external sphincter is not tonic though it contracts reflexly in the course of the flexion reflex and in synergy with the remainder of the abdominal parietes.

Regulation of Secretion and Motility.—It is now well recognized that hormones liberated from the mucosa of the small intestine play an important role in the regulation of secretion of the gastro-intestinal glands and of motility of the viscera.

The intestinal phase of gastric secretion results when many substances are introduced into the duodenum, *e. g.*, meat, meat extract and peptones. This effect may be due to: (1) secretagogs and/or (2) liberation of a hormone.

The inhibitory action of fats on gastric secretion and motility has been known for many years. An analysis of this action was made by Pavlov's pupil (Babkin[6]), and it was discovered that the neural and chemical phases of secretion could be inhibited by the introduction of olive oil into the duodenum. The existence of a chalone (enterogastrone) mechanism for the inhibition of gastric secretion and motility after the injection of adequate quantities of fats or sugars into the small intestine has now been demonstrated by several groups of investigators. The preparation of "enterogastrone" has been described by Gray, Bradley and Ivy.[34] Card[18] has been able to show that tannic acid preparations of "enterogastrone" are active in man.

In view of the fact that fat inhibits motility and secretion, the question naturally arises whether one or two chalones are involved. Lim[50] reviewed the evidence and came to the conclusion that only one chalone is responsible for the inhibition by fat of both gastric secretion and gastric motility. Ivy and his co-workers expressed agreement that the evidence points to the existence of only one chalone. At the same time they pointed out that conclusive proof that only one agent is responsible for both effects awaits the chemical isolation of the active principle or principles.

It has been demonstrated by Quigley and Meschan[68] that the introduction of fat into the duodenum also depresses duodenal motility, leading to a reversed gradient of pressure and some regurgitation without reversed peristalsis.

The onward flow of the gastric contents may be influenced also by the condition of the "fluid" in the duodenum. Gershon-Cohen and Shay[33] have shown that pyloric action is regulated by the physical stimulus of the hypotonicity or hypertonicity of fluids in the duodenum.

Spurrell[78] pointed out that the outflow from the stomach and the intragastric pressure are affected by the distention of the duodenum. Two reactions appear to be possible: (1) a positive distention effect, which closes the pylorus and reduces the rate of gastric outflow, and (2) a negative distention or drainage effect, which increases the gastric outflow by relaxation of the pylorus. The nerve path involved in these reflexes is limited to the splanchnic nerves.

It must also be remembered that stimulation of almost any afferent nerve may influence the state of the pyloric sphincter. Carnot[20] has found in the dog that the slightest uneasiness, excitement or fear would immediately close the pylorus and keep it closed for some time.

Again, hormonal mechanisms for the secretion of pancreatic duodenal and intestinal juices and for the contraction of the gallbladder and the villi have also been demonstrated. Little information is available of the reflex mechanisms which regulated the secretion and motility of the intestine.

It should be emphasized that the gastro-intestinal tract, though cut off from the central nervous system, is still capable of reacting to stimuli through its chemical and local nerve mechanisms. Local government exists, but central control has been abolished. The central nervous system has lost its power of adjusting the tissues in accordance with the needs of the body.

Pain.—Distention of the intestine can give rise to visceral pain. The pain is diffuse, poorly localized and often of a dull, boring character. It has been pointed out that the segmental distribution of the afferent neurones of the pupillo-dilator reflex supplying the small and large intestine are extensive. There is no evidence as yet to show that these fibers are "pain fibers." Theories which have been put forward to account for different phenomena are discussed in Lewis's monograph on "Pain."[49]

Readers are recommended to refer to Babkin's excellent monograph "Secretory Mechanism of the Digestive Glands" which has been published since this article was written.

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CHAPTER XXII

DISEASES OF THE SMALL INTESTINES

I. SYMPTOMS

Strictly speaking, all disorders of the small intestine are "functional" in the sense that normal function is deranged. It is, however, convenient to apply the adjective "organic" to those disorders which arise from morbid processes involving the small bowel itself, and the term "functional" to disorders arising secondarily to systemic disease, neurogenic influences or local lesions outside the intestine.

Pain, distention, audible peristalic noises, nausea, vomiting, diarrhea and constipation are the primary symptoms which characterize disorders of the small bowel. These symptoms are closely related to deranged transport of the intestinal content, and their proper interpretation requires an understanding of the factors which control the flow of material within the gut's lumen. The usual practice is to correlate the transport of chyme with particular types of small intestinal motor "waves." If chyme were solid or nearly so, such a correlation would be correct. Chyme, however, is a fluid substance the flow of which is dependent on intraenteric pressures.[6] To be sure, the intraenteric pressure in any intestinal loop is markedly influenced by the local motor activity of the bowel; but it is also modified by the intra-abdominal pressure, by the amount and consistency of the intestinal content and by those forces which tend to prevent the expulsion of this content into adjoining loops. A large wave of the peristaltic type (Chapter XXI), for instance, tends to raise intraluminal pressures and to push chyme down the intestine. If, however, a complete obstruction lies just distal to the peristalic wave, a high head of pressure develops between wave and obstruction. Only two eventualities are then possible: either the viscus is ruptured, or, as usually happens, the chyme flows backward toward areas of lower intraluminal pressure lying proximal to the peristaltic wave. Thus it is apparent that a powerful wave traveling down the bowel can, under the proper conditions, actually propel the intestinal contents toward the mouth,[21] and it is not necessary to postulate the existence of "reverse peristalsis," a type of motor activity which the normal and even the obstructed human intestine rarely exhibits.[2]

The sustained or basal pressure within the small bowel of a man in the supine position usually varies between +5 and +10 centimeters of water. With increased motility, temporary pressures of 20 to 60 centimeters of water develop, but these high pressures subside within one or two seconds as the contents of the loop are propelled onward.[6a] In disease, a deranged and uncoördinated motility pattern may occasion abnormally high pressures, moderately elevated pressures of long duration or pressure gradients favoring an abnormal transport of contents.[91]

Pain arises in the small bowel from only one stimulus: a strong contraction.[61] When the intestinal wall is stretched by an excessive intraluminal pressure or is irritated by some noxious agent, it contracts violently in repeated attempts to expel the offending contents. Each contraction causes a severe cramplike pain which is usually referred centrally and anteriorly to the umbilicus or just above it. If the pain spreads, it involves both sides of the abdomen symmetrically, irrespective of the location of the responsible disorder. Lewis[61] said: "Accurate localization is fortuitous." The pains, being synchronous with the contractions, occur intermittently at varying intervals, and are usually of one-half to one minute's duration. The intensity of the pain is proportional to the speed with which the intravisceral tension develops and the height which it attains; it is usually inversely proportional to the total duration of the disorder.

When the peritoneum is involved by disease originating in the small bowel, whether vascular infarction, neoplasm or inflammation, a different type of pain ensues. This pain is distinguished by two facts: (1) it can be directly localized, and (2) it is persistent, without the periodic fluctuations characteristic of contraction pains.

Distention.—Mechanical distention occurs when an increased intraluminal pressure develops behind an obstruction and gradually stretches a normal intestine; functional distention results from a primary failure of the bowel to maintain its normal motor functions, particularly its tone. Both types are attended by complicating factors which increase the accumulation of gas and liquid in the affected bowel. Obviously, the intestinal contents which normally are transported downstream tend to collect in the dilated loops. In addition, the increased tension within a stretched bowel wall impedes the flow of blood, and that moiety of gas and liquid which usually passes through the intestinal mucosa into the blood stream also remains within the lumen. Finally, the distended intestine secretes more succus entericus than it does under normal conditions,[48] and the supply of gas is augmented by aerophagia and by fermentation.[91a]

Nausea and Vomiting.—As far as the small intestine is concerned, nausea appears to be attended by a duodenal spasm which forces the duodenal contents back into the stomach.[53] Below the duodenum, the aboral flow of contents may be hastened.[14] A functional disorder of the bowel may therefore be produced by anything which causes nausea, commonly painful episodes involving the viscera, use of drugs, ocular and labyrinthine irritations, severe headaches, emotional disorders and increased intracranial pressures. If these stimuli are strong enough, functional vomiting occurs. The vomitus, as may be seen from the foregoing discussion, contains material from the upper part of the small bowel.

Under certain conditions, such as an advanced ileal obstruction, the combination of generalized distention and reversed intraluminal pressure gradients permits the stomach to become filled with material backing up from the ileum. Mechanical vomiting without much nausea thereupon takes place, much as it does in the presence of pyloric obstruction.

Borborygmi are audible peristaltic noises which occur when a gross mixture of gas and fluid is agitated in the bowel. Normally they may arise from the colon, but they are produced in the small intestine under conditions characterized by active motility and excessive accumulations of gas—mechanical distention, for instance.

Constipation and Diarrhea.—Although compensatory activity by the colon may mask abnormal transport in the small intestine, a markedly accelerated or retarded flow of contents in the small bowel is usually reflected in the nature and frequency of the stools. A complete organic obstruction of the small gut obviously is characterized by pronounced constipation. The same symptom may be present with partial obstruction, but frequently material on the distal side of the obstruction flows rapidly through the intestine and causes diarrhea.

With functional disorders, the rate of transport depends not on any single factor, but on the total motility pattern. A high tone retards transport almost as effectively as complete atony, for no matter how frequently peristaltic waves may occur, their effectiveness is reduced by the lack of "diastole" between waves.[3] Conversely, a few peristaltic waves traveling down a relatively atonic gut may initiate rapid transport. The coördination, or the lack of it, between adjoining intestinal segments also influences transport.[11] A peristaltic rush may carry chyme for considerable distances when a coördinated motility obtains, but large waves in one loop and spasm in the next are clearly inimical to free flow.

II. SIGNS

The physical signs possibly resulting from disease of the small intestine are distention, alteration in the frequency and character of peristaltic noises, visible peristalsis, abdominal masses, tenderness and spasm. Of these, distention and its significance have been discussed, while the implications of an abdominal mass are self evident. Marked tenderness and involuntary muscular spasms usually result from impulses arising in the mesenteric and parietal peritoneum and suggest involvement of these surfaces. On the other hand, probably some tenderness may occur from pressure on intravisceral lesions or from the palpation of contracted abdominal muscles.[61]

Intestinal motor activity normally produces intermittent but continual bursts of fine, cracking noises, which can be heard by applying a stethoscope to the abdomen. In the presence of a diarrheal state, these sounds are loud and frequent; in functional distention, the "quiet belly" is characteristic; in mechanical distention, peristaltic noises are pronounced, but their usual low-pitched crackle becomes a high-pitched tinkle as the taut bowel wall is increasingly stretched. Hyperactive peristalsis on the part of the small bowel also may make itself visible as a directionless, writhing movement near the umbilicus, but visible peristalsis usually means that the abdominal wall is thin or that the intestine has become hypertrophied during a chronic disorder.[91a]

Systemic Effects of Disorders of the Small Intestine.—The small bowel is so vital to the body's economy that all but its mildest disorders are attended by systemic manifestations. During acute disease, dehydration, loss of salt and shock menace the patient's life; with chronic conditions, various aspects of malnutrition appear. The small gut during acute disease—such as infarction, obstruction or severe diarrhea—not only fails to absorb ingested liquids but actually may lose as much as 3 to 6 L. of gastrointestinal secretions in twenty-four hours. The salt loss also may be prodigious. Juices aspirated from the small intestine contain 0.6 per cent sodium chloride;[1] hence, a patient with obstruction of the small intestine who vomits 4.5 L. loses as much salt as is contained in his plasma at any one time! If such losses in water and salt are not compensated, plasma volume drops; renal function is impaired; noxious agents circulate in the blood stream, and shock sets in.

Although dehydration and toxemia *per se* can be fatal, animal experiments and clinical observations indicate that distention as much as any other factor leads to serious consequences. For example, it causes a reduction in plasma volume greater than can be accounted for merely on the basis of dehydration.[35] It diminishes the venous return to the right side of the heart by damming up blood in the vessels of the mesentery and of the lower extremities.[91a] Finally, it may permit the passage of noxious agents, as yet unidentified, through a mucosa damaged by stretch and anoxemia. Distention, dehydration and reduced blood volume are some of the complicating factors which may cause a disorder of the small bowel to terminate fatally; they are *the* factors which are relatively amenable to proper therapy.

In chronic disorders of the small gut, the absorptive capacity may be impaired by a variety of mechanisms. The available absorbing surface, though normal, may be sharply curtailed in area by a diffuse disease or by a surgical procedure,[13] or it may be normal in area but abnormal in function, a condition which holds true in the presence of sprue and in the chronically dilated intestinal loops which develop behind a partial obstruction. Whatever the mechanism, the absorption of fats, proteins, sugars and vitamins is decreased. Since fats are normally absorbed more slowly than other foodstuffs, fecal loss of lipids (steatorrhea) is particularly marked and brings about a deficiency of the fat-soluble vitamins A, D, K and E. When function of the small intestine has been impaired by disease or surgical measures, deficiencies in the vitamin B complex develop, [37] or, for unknown reasons, normal red cell maturation is inhibited.[17]

III. DIAGNOSIS

Through the signs and symptoms of disorders of the small intestine are suggestive, they are not exclusively specific, and except when the condition is full-blown, various laboratory procedures are necessary to establish the diagnosis. The most informative of these procedures are: (*a*) fecal analysis, (*b*) roentgenologic examinations and (*c*) intubation of the small intestine.

Fecal Analysis.—A fresh fecal specimen is examined grossly for its color, its consistency and the presence of particularly offensive odors. A search for blood, either in gross or occult form (guaiac test), is a routine necessity. The specimen is examined microscopically for white and red blood cells, undigested food residues, evidences of parasitic infestation, fat droplets (Sudan III stain) and starches (Lugol's solution).

Roentgenologic Examination.—A flat plate of the abdomen should always be made first.[81] The primary objective of this is to determine whether gas shadows are present in the small intestine, for the demonstration of such shadows in an adult is indicative of a functional or organic disorder of the small gut. Obviously the importance of this finding is modified by the amount of gas, its persistence and the extent of its distribution. If gas is demonstrated, it must be differentiated from that which normally occurs in the stomach and colon. In the presence of severe distention affecting either the large or the small bowel, this may be impossible, but otherwise little difficulty should be experienced in differentiating the serrated jejunum and even the ileum from the uneven colonic gas shadows, which usually show the characteristic haustral markings. In general, localized collections of gas speak for an organic disorder, whereas gas scattered throughout the intestinal tract suggests a functional abnormality.

If the information obtained from the abdominal flat film is inadequate, a barium enema may be given to localize intestinal gas shadows and to evaluate the status of the colon. In most instances this procedure is not harmful, but when localized intraperitoneal inflammation or ischemia is present, an enema may break down the localizing process and lead to spreading peritonitis.[91a]

Barium should not be given by mouth when jejunal or ileal obstruction is suspected. Not only may such a procedure increase the degree of obstruction, but it will yield little information. The barium, diluted by the intestinal content stagnating behind the obstruction, becomes distributed in many dilated intestinal coils, which overlie the lesion and obscure both its nature and its location. These difficulties may be avoided by intubating the small intestine with a Miller-Abbott tube.[5] The inflated balloon will not pass an obstructing point and will come to rest just proximal to the lesion, where, after complete aspiration of intestinal contents, a thin suspension of barium may be injected. The precise location of the obstructing point, and in many cases its exact outlines, can be defined by this technic.[7] If necessary, the injected barium may be aspirated after completion of the examination. While intubation of the small intestine is rather tedious, it should be remembered that in many cases it serves therapy as well as diagnosis.[8] Even when the disorder is mild or chronic and does not require immediate intestinal decompression, the Miller-Abbott tube can be used diagnostically, either to inject barium locally or to obtain a record of the intestinal contractions. For the latter purpose it is necessary to attach a kymographic device to the lumen leading to the balloon.[9]

When obstruction beyond the ligament of Treitz is unlikely, a barium meal may be given and the pattern of the small intestine studied at hourly intervals by roentgenography and fluoroscopy until most of the meal is in the colon. By this technic, local defects of the upper part of the small intestine and generalized abnormalities in motility can be readily identified.[38] On the other hand, the reduplication and overlapping of the intestinal coils and the long intervals between observations make the identification of a lower jejunal or an ileal lesion more or less fortuitous.

Better than giving a barium meal is "barium enteroclysis." The duodenum is intubated and a dilute suspension of barium sulfate is injected. This barium normally reaches the cecum within ten to fifteen minutes, a period brief enough to permit continual fluoroscopic observation of the advancing column of opaque material.[36]

IV. ACUTE OBSTRUCTION OF THE SMALL INTESTINE

An episode characterized by the sudden arrest of intestinal transport is usually called an acute obstruction, or ileus. The following terminology will be used here:

I. Organic Obstruction (mechanical obstruction, mechanical ileus)
    A. Simple
    B. Anoxemic (strangulation obstruction)

II. Functional Obstruction
  A. Inactive (paralytic ileus, adynamic ileus, adynamic obstruction, inhibition ileus)
  B. Active (dynamic ileus)

Simple Organic Obstruction.—Acute organic obstruction of both large and small bowel is encountered approximately once in every 400 hospital admissions. In three-fourths of these the small gut is involved, and ileal obstructions outnumber those of the jejunum and duodenum in a ratio of 10 to 1. As is shown in Table 8, by far the most common causes of sudden occlusion of the small bowel are bands, adhesions and external strangulated hernias.[70] Since bands and adhesions frequently develop after operation, it is not surprising that 80 per cent of all acute organic obstructions of the small intestine, exclusive of strangulated external hernias, occur in patients with abdominal operative scars.[72]

TABLE 8.—CAUSES OF ACUTE ORGANIC OBSTRUCTION OF THE SMALL INTESTINE IN ADULTS

	Per cent
Strangulated external hernias*	40
Bands and adhesions*	40
Volvulus	5
Mesenteric thrombosis	4
Neoplasm (primary and secondary)	2
Intussusception	2
Acute infectious processes (diverticulitis, appendiceal abscesses, etc.)	2
Gallstones and other foreign bodies	2
Internal hernias	1.5
Regional ileitis	1
Meckel's diverticulum	0.5

* As a general rule, strangulated external hernias appear to be more frequent in rural districts; whereas in large urban centers, bands and adhesions are the most common cause of acute intestinal obstruction.

The cardinal symptoms of intestinal obstruction are pain, vomiting, distention and obstipation. The pain, typically intermittent colic, starts abruptly and is attended at first by functional vomiting. Later, the nature and the amount of the vomitus, as well as the degree of distention, depend on the site of the obstructing point. When this is in the duodenum or high in the jejunum, distention is slight, and mechanical vomiting of a watery, bile-stained material is early and copious. When the lesion is lower in the small intestine, on the other hand, considerable distention will usually have developed before the patient vomits a dark brown, muddy and possibly fecal fluid. When obstruction is colonic, distention is pronounced, but vomiting, except of a functional type, is not common. Regardless of location of the obstruction, the passage of stools and gas is diminished or abolished, roughly in proportion to the degree of occlusion. It must be remembered, however, that the expulsion of rectal flatus or fecal enema returns do not rule out an obstruction of the small gut.

Mild shock—with weakness, sweating and palpitation—frequently accompanies the initial cramps, particularly if the pain is severe. This shock is of the neurogenic type and does not differ from that which may be produced by any violent visceral pain. Later in the course of an unrelieved intestinal obstruction, shocklike manifestations are usually the deleterious results of distention and dehydration. At this late stage, when increasing anoxemia and toxemia impair the bowel's motility, the intermittent colics give way to a constant dull ache.

The patient with an acute intestinal obstruction is anxious and obviously ill. When seized by a colic, he turns and twists with pain, and loud gurgling noises may be heard in his abdomen. Abdominal ausculation confirms the fact that peristaltic activity and the intensity of the cramps wax and wane synchronously. If the outline of individual intestinal loops or peristalsis is visible, it is likely that the patient has had a preëxisting partial obstruction.[91a] Moderate and generalized abdominal tenderness is often elicited, but spasm, marked tenderness or a palpable mass does not usually accompany simple organic obstruction of the small bowel.

The temperature and pulse are normal or moderately elevated. Typically, the white cell count ranges between 8,000 and 12,000, while the erythrocyte, hematocrit and hemoglobin levels may be high, as a result of hemoconcentration. A rising fever, pulse rate and leukocytosis and a falling blood pressure suggests the development of complications like shock or strangulation of the obstructed bowel. In order to locate the point of obstruction, roentgen study of the abdomen with the patient lying down is of primary importance. To evaluate the systemic effects of the obstruction, determinations of plasma chlorides (usually low), plasma sodium (often low), carbon dioxide—combining power (variable), serum proteins (normal or high) and the blood nonprotein nitrogen (often elevated) must be made.

With proper treatment, the mortality in cases of simple organic obstruction is between 5 and 20 per cent.[59]

Anoxemic Organic Obstruction.—From the viewpoint of treatment, the differential diagnosis between obstructions with and without impaired intestinal circulation is most important. Unfortunately, this differentiation is difficult except when an acutely tender mass in an inguinal, femoral, umbilical or incisional orifice makes the diagnosis of strangulated external hernia obvious. If external hernias and the intussusceptions of infants are excluded, approximately one-third of the acute organic obstructions of the small bowel can be expected to interfere with the mesenteric blood supply. Mesenteric infarction, volvulus, intussusception and internal hernia account for many obstructions, but old adhesions may also strangulate the intestine by twisting and kinking the mesentery. The fibrinous adhesions responsible for early postoperative obstruction rarely compromise the circulation.

The pain which occurs in the attack has been known to rival that of perforated peptic ulcer. Subsequently the usual picture of obstruction makes its appearance, but not alone, for serosanguineous fluid exuding from the anoxemic loops evokes the signs and symptoms of peritoneal irritation.[49] As a consequence, the intermittent colics are accompanied or even replaced by a continuous, localized pain; and definite tenderness with spasm is elicited over the affected bowel (Table 9). A palpable mass develops in many cases. If unchecked, the process culminates in gangrene, perforation, peritonitis and death.

Systematically, the patient with a strangulating obstruction shows definite evidence of shock, inflammation and toxemia. The pulse is fast, the blood pressure low. A leukocyte count above 15,000 may be present initially, but more significant is a progressively rising count. Though the electrolyte balance may or may not be greatly upset, shock, renal failure and toxemia, as well as peritonitis, are responsible for the high mortality (40 to 50 per cent).

TABLE 9.—IMPORTANT FINDINGS IN THE THREE COMMON TYPES OF SMALL INTESTINAL OBSTRUCTION

	Simple, organic	Anoxemic, organic	Inactive,* functional
Pain	Severe, intermittent, vaguely localized	Intermittent colic superimposed on severe continuous localized pain	Moderate, continuous, not localized
Vomiting	Present, may be fecal	Present	Not always present, rarely fecal
Distention	Often present, may be localized	Usually present	Always present, diffuse
Obstipation	Usually present	Present	Present
Tenderness	Moderate, vaguely localized	Definite, localized	Moderate, not localized
Spasm	Usually absent	Often present	Absent
Borborygmi, peristaltic noises	Present	Often present	Diminished or absent
Abdominal film	Usually gas in dilated small bowel loops	Gas in dilated small bowel loops	Dilated large and small bowel loops

Special Types of Acute Organic Obstruction.—In closed loop obstructions, the bowel is organically occluded at two or more points, as in volvulus.[71] Other causes of multiple intestinal obstructions are the adhesions of peritonitis and peritoneal carcinimatosis, but the obstructive symptoms in these are often chronic rather than acute.

Internal hernia may develop when a loop of gut slips through a narrow opening in the peritoneum or mesentery.[86] Such an opening may occur about the duodenojejunal junction or cecum or in the sigmoid mesentery, where considerable individual variation in the peritonteal attachments of the bowel is likely to occur. Rarely internal herniation may occur in holes left in the omentum or mesentery by careless operative procedures.

Intussusception, particularly the "idiopathic" type, is primarily a disease of childhood. Adults are infrequently affected, usually (75 per cent) with some organic lesion at the head of the intestinal invagination. When the small intestine is involved, the responsible lesion is apt to be a neoplasm, a Meckel diverticulum or an inflammatory process.[28] Intussusceptions usually produce acute obstruction, but cases of chronic obstruction have been described.[41] It should be noted that the characteristic findings of intussusception in infants, a sausage-shaped mass and the expulsion of bloody mucus by rectum, do not necessarily occur in adults.[70a]

Functional Obstruction.—Active and inactive functional obstructions result from imbalance between those intestinal motor forces which promote and those which resist evacuation. The inactive variety is by far the more common and occurs when the propulsive forces are strongly inhibited by intestinal anoxemia or by adrenergic impulses which are reflexly activated and reach the bowel by way of its extrinsic nervous system.[91a] Many stimuli may activate this inhibitory reflex, but the most important in order of frequency are: operative trauma to the intestines, peritonitis, overwhelming infections, severe visceral pain, use of drugs and spinal injuries. After the initial inhibitory influences have subsided, the bowel may remain distended and inactive, but its motor activity returns after successful decompression with the Miller-Abbott tube.

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* The typical findings may be altered by the primary disease, such as peritonitis.

Whereas it takes at least three or four hours for clearcut distention to develop behind an organic obstruction, the reflex mechanism set in motion by a visceral pain can produce dilated and atonic intestinal loops within a few minutes. The functional obstruction which occurs postoperatively or as a result of peritonitis develops more slowly but may culmination massive distention with no evidence of any muscular activity on the part of the bowel. The diagnostic criteria by which such an obstruction is recognized (Table 9) are usually unmistakable, but in some cases the picture is confused by the signs and symptoms of the primary disorder.

Active functional obstruction is rare. It appears when motor forces which resist evacuation, such as spasm, block the intestinal lumen in spite of strong but often abnormal peristaltic activity. The differentiation from an organic obstruction is obviously difficult and can be achieved preoperatively only by intubation. An anoxemic functional obstruction is also unusual, but in some cases persistent and marked distention of the intestinal wall, combined with a reduction of arterial pressure and venous flow by shock, may impair the intestinal circulation critically.

The distinction between functional and organic obstruction is at times rendered academic by borderline or mixed disease. Mesenteric infarction, for instance, is doubtless organic; yet it may bring about functional dilatation rather than organic narrowing of the intestinal lumen. As a result of the pain or the peritoneal irritation of a strangulating obstruction, the bowel may relax instead of fighting the obstruction with violent peristalsis. Even a simple organic obstruction of long duration will slowly become predominantly functional. These considerations, however, do not invalidate the clinical usefulness of attempting to recognize the different types of intestinal obstruction.

The Treatment of Acute Obstruction.—Only the general principles of treating an acute intestinal obstruction will be outlined here. Though presented here dogmatically, these principles are still debated in many quarters.

1. Dehydration, starvation and an abnormal acid-base balance should be corrected by infusions of physiologic saline solution containing 5 per cent dextrose. Hemoconcentration and/or shock must be corrected by transfusions of plasma or whole blood.

2. As soon as the patient's blood volume and constituents have been corrected, immediate operation is indicated in the following conditions:
   - A. Any obstruction of less than twenty-four hours' duration;[73]
   - B. Any obstruction of less than forty-eight hours' duration if distention is slight and the patient's general condition good;
   - C. Any anoxemic (strangulating) obstruction;
   - D. Any obstruction of the large bowel.

Intubation of the small intestine may be attempted before operation in order to maintain decompression subsequently, but no more than one hour should be spent in the effort.

3. Intubation is indicated in the following conditions:
   - A. Any functional obstruction (active or inactive);
   - B. Any small intestinal obstruction (except the anoxemic type) of more than forty-eight hours' duration;
   - C. Any small intestinal obstruction of more than twenty-four hours' duration, if the patient has marked distention or is in poor condition.

Repeated attempts should be made to intubate the small intestine under fluoroscopic control. Operation should not be carried out before successful decompression, for it is considerably less risky to move the patient repeatedly to a fluoroscope than to carry out a decompression operation in the presence of massive distention and toxicity and under the threat of shock.

For functional obstruction or occasionally for organic obstruction by early postoperative adhesions and edema, no further therapy is needed after successful decompression with the Miller-Abbott tube.

Inhalations of 95 per cent oxygen may be given intermittently for distention which cannot be relieved otherwise.[34] For inactive functional obstructions not caused by peritonitis, prostigmine, pituitary extract and ergotamine may rationally be used.[16]

V. CHRONIC OBSTRUCTION OF THE SMALL INTESTINE

Chronic obstructions of the small bowel are usually produced by granulomatous and neoplastic processes which slowly encroach on the intestinal lumen. Much less commonly, a band, an adhesion or a congenital anomaly may cause stenosis of the bowel; and occasionally chronic obstructive symptoms follow ill-considered enteroenterostomies and functional disorders.

The symptoms and signs are similar to those of acute obstruction, but milder and of longer duration, sometimes for years. Intermittent crampy pain associated with evidences of intestinal hyperactivity is again the symptom of paramount significance. Vomiting is prominent if the lesion is near the stomach; with lower obstructions, this symptom and distention occur sporadically. Either diarrhea or constipation may predominate, depending on the nature of the lesion, its site and the degree of enterostenosis. Thus, an extensive inflammatory process such as regional ileitis typically produces loose, frequent stools; whereas a narrow, annular, constricting lesion with little inflammatory reaction makes the patient resort to frequent enemas.

The patient with a chronic partial obstruction is tired and emaciated; not only may his intestinal absorptive capacity be impaired, but he suffers from anorexia and has learned that his symptoms are milder if his food intake is limited. Visible peristalsis is evident as a rule. Anemia, usually hypochromic but occasionally hyperchromic, occurs because of deficient iron intake, poor absorption or actual bleeding from the obstructing point. In the blood, low protein and vitamin levels reflect the malnutrition; and when the condition is advanced, clinical evidence of vitamin deficiencies and hypoproteinemia (*i. e.*, edema) may be apparent.

VI. MESENTERIC VASCULAR OCCLUSION

In 2 of 3 cases, mesenteric infarction is brought about by venous thrombosis; in the third, arterial embolism or thrombosis is causative.[94] Since massive thrombosis is often agonal, and mild thrombosis may go unrecognized, the true incidence of this condition is hard to compute. Table 8 shows the frequency of symptoms of organic obstruction, but probably no more than one-half of all mesenteric occlusions are included in this group. As might be expected, the disease generally occurs in patients over forty.

Embolism to the superior mesenteric artery or its branches (the inferior mesenteric artery is rarely involved) is the result of bacterial endocarditis, auricular fibrillation or coronary occlusion. Arteriosclerotic plaques are held responsible for arterial thrombosis.[80] The causes of venous thrombosis are more diverse: inflammatory or malignant disease of the intestinal tract, trauma, portal stasis, strangulating obstructions and blood dyscrasia.

Abdominal operations, however, account for mesenteric thrombosis in over one-third of the cases.[94a]

Pain—pain which is severe and continuous but which often undergoes colicky exacerbations—overshadows all other symptoms of mesenteric vascular occlusion. Vomiting, constipation or, less frequently, diarrhea, bloody stools and progressive distention may occur. With severe involvement, the evidences of shock are marked, not only because of violent visceral pain but because of loss of blood into the infarcted bowel.

The physical examination reveals prostration with moderate abdominal tenderness and rigidity. Peristaltic sounds are usually present. Rarely a mass is palpable. The pulse and blood pressure reflect the degree of shock; the temperature is normal or subnormal. Considerable importance has been attached to the high leukocyte count, usually between 15,000 and 25,000, although counts from 5,000 to 50,000 have been recorded. The abdominal roentgenogram shows variable gaseous dilatation of both large and small bowel.

With the exception of pain, the symptoms, signs and laboratory findings of mesenteric vascular occlusion are undependable. Nevertheless, a violent abdominal pain accompanied by early symptoms of shock in an elderly patient who has recently undergone an operation or who is known to have intestinal disease should suggest this condition, especially if peristaltic sounds are heard and abdominal rigidity is comparatively moderate. Acute pancreatitis and strangulated intestinal obstruction, it is true, present particular difficulty in differential diagnosis, but bloody stools or vomitus will, if present, point to mesenteric infarction.

There is no doubt that recovery from minor mesenteric thrombosis is possible.[64] Even extensive venous occlusion is compatible with life if the process has advanced slowly enough to permit the development of anastomoses. When the disease is acute, however, the mortality is over 90 per cent. The only therapeutic hope lies in early diagnosis and surgical resection of the infarcted bowel.

VII. NEOPLASMS OF THE SMALL INTESTINE

The incidence and average distribution of the three major types of neoplasms of the small intestine is shown in figure 99.[82] Malignant tumors may reach considerable size, are usually single and spread by lymphatic metastasis or direct invasion. They occur slightly more frequently than the benign growths, which are usually (but not always) smaller, often polypoid and sometimes multiple.[82a] Carcinoma is particularly frequent in the periampullary region of the duodenum, but considerably less frequent above or below the papilla of Vater: Only 47 cases of carcinoma of the infrapapillary duodenum have been reported.[33] The commonest malignant growth of the small intestine in young adults is lymphoblastoma (lymphosarcoma, lymphoma, Hodgkins); in patients past forty, carcinoma predominates. Sarcoma is rare. Of the benign lesions, adenoma, myoma and lipoma are the most common, but fibroma, hemangioma, chylangioma, pancreatic rest, cyst and carcinoid (argentaffin tumor) are also found.

All the malignant and about one-half the benign growths give rise to symptoms. Bleeding, pain and evidences of obstruction occur singly or in combination, but the variable locations and characteristics of neoplasms in the small intestine militate against a uniform clinical picture.[42] Occasionally, a mass is palpable. Carcinoma, which slowly enlarges and ulcerates, tends to produce chronic blood loss, the symptoms of chronic obstruction and pain. If the cancer is in the duodenum, the pain is boring and may, in its response to alkalis, resemble that of duodenal ulcer. Lymphoblastoma is somewhat less apt to ulcerate and does not usually cause melena, but often obstructs either by constricting the lumen or by rendering the bowel wall rigid and fixed.[89]

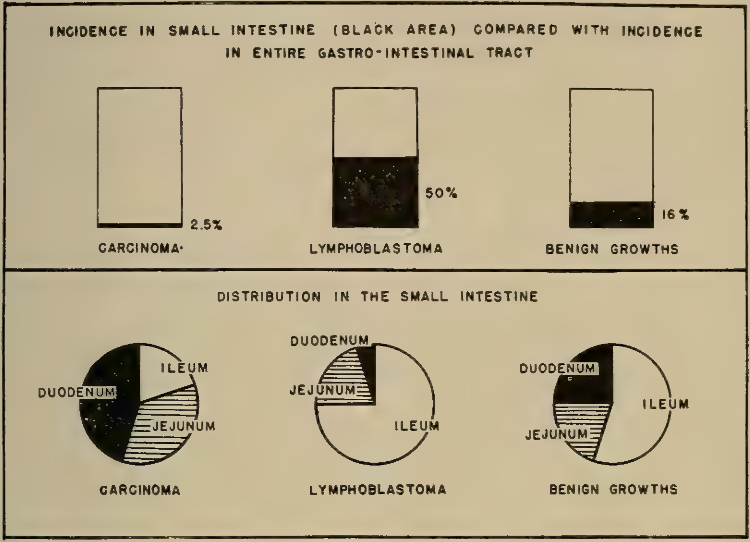

Figure 99

A benign growth often manifests its presence by precipitating acute episodes. A myoma, hemangioma or strangulated polyp may be responsible for a severe intestinal hemorrhage, and any benign neoplasm may serve as the leading point for an intussusception.[75] Lipoma, for example, is said to cause intussusception in 16 per cent of the reported cases.[24]

After the appendix, the ileum is the most frequent site of carcinoids. Usually these are benign, but about one-third are multicentric, and in one-fifth of argentaffin tumors of the small intestine metastases occur.[50] Whether malignant or not, however, they do not ulcerate through the mucosa. Occasionally other benign neoplasms, particularly multiple polyps, also are subject to malignant change.

The secondary malignant growths of the small bowel arise most frequently in the stomach, pancreas, uterus and ovary.[82a] Endometrial implants, which may obstruct the rectosigmoid, rarely produce stenosis of the small intestine.[74] These lesions are of diagnostic interest, however, for in some cases the obstructive symptoms reach their peak with each menstrual period.

The prognosis of carcinoma of the small intestine is poor because of the prevalence of metastases. Lymphoblastoma is more amenable, both to surgical removal and to irradiation.

VIII. GRANULOMATOUS DISEASES OF THE SMALL INTESTINE AND MESENTERY

Of the granulomatous diseases affecting the small bowel and its mesentery, regional ileitis and the related jejunoileitis are the most common (Chapter XXIII). Tuberculous enteritis (Chapter XXIV) is seen not infrequently, but syphilis and actinomycosis are rare. Intestinal lipodystrophy (Whipple's[93] disease) is rare. In this condition, the intestinal and mesenteric lymphatic tissues become loaded with abnormal lipid deposits, which appear to stimulate a fibrotic reaction. As a consequence, the patient exhibits steatorrhea and the symptoms of chronic obstruction.[84] Pneumatosis of the intestines is the name give to a rare entity characterized by the presence of multiple air-filled cysts in the subserous layer of the bowel and the mesentery.[20] Occasionally nonspecific degenerative and chronic inflammatory changes occur in the small intestine after prolonged irradiation over the abdomen.[79]

IX. MECKEL'S DIVERTICULUM

In 1.8 per cent of males and 0.8 per cent of females, the embryonic vitelline duct connecting the yolk sac to the midgut does not atrophy, but remains open at its intestinal end to form the cul de sac known as Meckel's diverticulum.[47] Of variable length, this diverticulum usually arises from the antemesenteric side of the ileum at a distance from 25 to 100 centimeters above the ileocecal valve. Its lumen is lined with ileal mucosa, but heterotopic tissue such as pancreatic rests and gastric, colonic and duodenal mucosa may also be present.[32]

Intestinal obstruction is the chief complication which Meckel's diverticulum precipitates in adults.[78] Congenital bands, adhesions and inflammatory masses resulting from chronic Meckel diverticulitis and volvulus account for most of the obstructions. In many cases, however, the attack is precipitated or accompanied by an acute inflammation of the diverticulum. As a consequence, the clinical picture is that of acute organic obstruction of the small bowel plus such signs of inflammation and peritoneal irritation as may stem from an acute diverticulitis.

Simple acute diverticulitis, the second most frequent complication in adults,[78] occasions signs and symptoms similar to those of acute appendicitis. Pain, tenderness and rigidity near the umbilicus and evidences of intestinal obstruction such as colicky pain and distention may point more to diverticulitis than to appendicitis, but the differential diagnosis is difficult.[95] Perforation of the inflamed diverticulum is always a danger.

Peptic Ulcer.—Since in 16 per cent of cases Meckel's diverticulum is said to contain islands of gastric mucosa, it is not surprising that peptic ulcer develops in the ileal mucosa at the orifice of the diverticulum.[92] This complication, however, occurs chiefly (over three-fourths of cases) in patients under fifteen. Postprandial pain resembling that of duodenal ulcer is occasionally present, but usually the diverticular ulcer manifests its presence by perforating or by giving rise to severe intestinal hemorrhage. Peptic ulceration of Meckel's diverticulum must be seriously suspected in boys who complain of pain in the lower part of the abdomen and who pass dark clotted blood by rectum.

Intussusception due to Meckel's diverticulum is also more common in the younger age group, only one-fourth of the cases occurring in patients over twenty.[47a]

Neoplasms, both benign and malignant, may originate in Meckel's diverticulum.[12] In many of the intussusceptions caused by this organ, a tumor is found at the head of the invaginated diverticulum.[47a]

X. ACQUIRED DIVERTICULUMS

The so-called acquired diverticulums of the small intestine occur as herniations of the mucosa through such weak points in the intestinal wall as are present at the papilla of Vater and at the points where bloodvessels enter the gut.[27] Of all acquired intestinal diverticulums, 18 per cent are said to occur in the duodenum, 6 per cent in the jejunum, 1.5 per cent in the ileum and the rest in the large bowel.[26] Certainly duodenal diverticulums are frequent,[10] being demonstrable in 5 per cent of all gastrointestinal *x*-ray studies. Usually they are single and project medially from the descending duodenum. Jejunal diverticulums are rare, are commonly situated on the mesenteric border and tend to be multiple.[83] In several cases more than 200 have been reported.[46]

As a general rule. diverticulums of the small bowel cause no symptoms and should not be held responsible for functional complaints. On occasion, however, a large diverticulum may cause pain and mild obstructive symptoms. Diverticulitis of the small intestine is rare.[25]

XI. SPRUE

Tropical sprue, nontropical (idiopathic) sprue and the celiac syndrome (Gee-Herter disease) of children are diseases of the small intestine characterized by functional motor disorders and impaired absorption of foods, particularly fats. Whether these three conditions represent different aspects of the same disease is a matter of dispute,[88] but for clinical purposes, tropical and nontropical sprue can be discussed under one heading. The celiac syndrome will not be considered here.

The origin of sprue is unknown. Some believe it to be an infectious disease;[15] others favor the theory of glandular dysfunction,[90] but the preponderant opinion is that sprue is caused, or at least conditioned, by an unidentified vitamin deficiency.[65] Whoever wishes to ascribe sprue to one cause must contend with the facts that sprue is endemic in certain tropical areas, that the initial symptoms may appear years after the patient has left the tropics and that the nontropical variety occurs in patients who have never been outside temperature latitudes.[88a,b]

Patients who die of sprue often exhibit atrophy of the intestinal mucosa and musculature, as well as round cell infiltration of these tissues and the mesenteric lymph nodes. Such morbid changes, however, are probably nonspecific.[88] Attention has been drawn also to the degeneration which affects the intrinsic nervous system of the bowel, for this finding forms the basis for the plausible hypothesis that sprue is primarily a disease of the nerve plexuses which regulate the functions of the small intestine.[54]

During sprue, the intestine is markedly atonic, but large peristaltic waves and stationary spasms occur irregularly at scattered points.[54a] Symptomatic evidences of this disorganized motility are diarrhea, cramps and meteorism. Typically, the diarrheal stools are pale, greasy, unformed and foul, but watery or semiformed stools occur in many cases. Cramps and distention are of variable intensity, sometimes severe enough to give the picture of an active functional obstruction.[52a] Nausea and vomiting are late manifestations.

Absorption in sprue is impaired, partly because of the marked motor abnormalities.[68] Some authorities have ascribed the poor lipid absorption to a depressed pumping action on the part of the villi.[51] Others have blamed intestinal edema or the dysfunction of an unidentified enzyme, although the known pancreatic enzymes are not deficient in the presence of sprue.[88] It must be emphasized, however, that not only fats,[18] but all foodstuffs[31] are poorly absorbed. As a consequence, the patient with sprue becomes emaciated no matter how much he eats. Muscles and skin waste away, bringing the cheek bones into prominent relief. Probably because of poor nutrition, clubbing of the fingers[52] and a spotty brown pigmentation (melanin?) of the skin may develop.[56]

Specific deficiencies, particularly of the fat-soluble vitamins (A, D, K and E) appear secondarily; or, as often happens in the nontropical form, these deficiencies may account for the patient's chief complaints.[52a] Hypocalcemic tetany and osteoporosis occur frequently, more from the inadequate absorption of vitamin D than from the formation of insoluble calcium soaps in the lipid-rich intestinal contents.[19] Like vitamin D, vitamin K is poorly absorbed, and purpura, bleeding gums or hematuria may suddenly develop.[55] Vitamin A deficiency, easily demonstrable by laboratory methods,[67] is usually not obvious, but careful investigation may reveal night blindness, xerophthalmia and hyperkeratosis about the hair follicles. Impotence, if present, may be the result of inanition rather than of vitamin E deficiency.

A smooth, fiery red tongue, fissures at the corners of the mouth, aphthous stomatitis and sometimes a full-blown picture of pellagra (see Chapter XLVII) are ample evidence that the patient with sprue may also suffer from a B complex deficiency.[65a] As a rule, the lack of vitamin B complex is common with tropical sprue, whereas the lack of vitamins A, D and K is more striking with the nontropical variety.

Laboratory studies emphasize the defects of intestinal motility and absorption. The stools contain an abundance of fat, little mucus and rarely white or red cells. Gastric analysis reveals hypoacidity in most, and anacidity to histamine in one-fourth the cases. Marked anemia is characteristic. In the tropical variety, this tends to resemble the macrocytic picture of pernicious anemia,[23] but hypochromic, microcytic anemia also is encountered. An oral dextrose tolerance test yields a flat curve, but the intravenous test gives near normal results.[31b] In the blood, the levels of calcium, phosphorus and cholesterol are low, and the prothrombin time may be abnormally prolonged. The plasma content of vitamin A is depressed, but more significant from the diagnostic point of view is the extremely low carotene level. Roentgenograms of the small intestine show that the barium moves along the gut in thick, sausage-shaped masses; that many of the loops of small bowel are dilated and often contain gas, and that the usual fine markings of the "valvulae conniventes" are thickened, widely separated and sometimes completely obliterated.[85]

Sprue, if untreated, runs a chronic course with remissions and exacerbations, until the patient dies of inanition or some complication.[76] For advanced disease, intensive treatment keeps the patient alive and corrects the vitamin deficiencies, although the intestinal symptoms may persist.[44] For milder involvement, treatment is often remarkably successful,[77] but it must be maintained in modified form throughout the patient's life.

The diet should be moderately bland, extremely low in fat (50 Gm. or less) and high in proteins (120 Gm. or more). Enough carbohydrates must be given to bring the intake of calories above 2,500 per day, simple sugars being preferable to starches. At first, 5 cubic centimeters each of a crude (1 unit per cubic centimeter) liver extract and of a vitamin B complex preparation should be given intramuscularly every day. Later the size and frequency of the doses can be reduced. About 20,000 units of vitamin D and 100,000 units of vitamin A are given daily by mouth. Vitamin K (1 mg.) is given parenterally once a week. The calcium intake can be increased with skimmed milk and calcium lactate tablets. Ferrous sulfate may be given if it does not aggravate the intestinal symptoms.

XII. FUNCTIONAL DISORDERS

About ten years ago, roentgenologists began to notice an abnormal pattern of the small intestine which is characterized by gas shadows, clumping of the radioöpaque contents and coarsening of the mucosal markings. These changes, first observed in patients with vitamin deficiencies, were grouped together under the name "deficiency pattern."[63] It is now known, however, that motor disorders of the small intestine which give rise to the "deficiency pattern" are not specific but functional, and are induced by a great variety of stimuli.[87] Some of these functional disorders are severe enough to occasion definite symptoms and signs of disease of the small intestine;[60] others are clinically silent and are apparent only when the small bowel is studied with the x-ray or by intubation. The principal causes of functional disorder of the small intestine will be discussed later.

Vitamin Deficiencies.—Among other effects, advanced vitamin deficiencies bring about morbid changes in the nerve cells of the intestines.[69] It is therefore reasonable to suppose that the intrinsic plexuses of the bowel may, in the presence of a moderate deficiency, undergo mild and reversible degenerative processes or may merely function abnormally.[62] In such a case intestinal motility becomes disorganized and gives rise to the "deficiency pattern," even though the organic changes of severe vitamin deficiency have not yet made their appearance. Treatment with the necessary factors, usually members of the vitamin B complex, should restore normal motor function when involvement is in the early stage.

Anoxemia.—It has already been indicated that mesenteric occlusions or strangulating obstructions induce severe disturbances in intestinal function. Considerably less dramatic but definite functional changes are often encountered in conditions of chronic intestinal anoxemia, such as cardiac failure, portal stasis and marked anemia.

Direct or reflex stimulation of the bowel's extrinsic nerves produces motor disorders which in their extreme form are exemplified by inactive functional obstructions. Lesser responses attend weaker stimuli. Calcified mesenteric nodes, though commonly thought to be of no significance, may, for example, alter the normal roentgen pattern of neighboring intestinal loops.[39]

Emotional and psychic factors undoubtedly disorganize intestinal motor function. Striking changes sometimes occur in the motility record taken from the human small bowel if the subject becomes unduly upset,[2] and even an angered rat exhibits an abnormal intestinal pattern.[38] Both clinical and experimental observations seem to indicate that the descending portion of the duodenum is particularly sensitive to neurogenic influences. Here barium is seen to churn back and forth in a neurasthenic person subjected to gastrointestinal fluoroscopy. Here, too, marked spasm may occur during nausea;[53] and some common epigastric complaints, such as fulness and burning, are possibly more often duodenal than gastric in origin. Lower in the small bowel, emotional stresses may induce enough hypermotility to cause diarrhea,[40] and the symptoms produced may mimic those usually ascribed to the "irritable colon."[30] Up to the present, however, the nature of the psychogenic stimuli and the character of the intestinal responses have not had the benefit of such careful studies as have been made on the relation between the psyche and gastric function.*

Metabolic diseases are often responsible for disorders of intestinal function. The abdominal signs and symptoms accompanying diabetic acidosis or Addisonian crises, it is well known, have been erroneously diagnosed as indicating a "surgical belly." Disorders of the porphyrin metabolism, such as acute porphyria[66] and lead poisoning, can produce violent colic and give the picture of an active functional obstruction.[91a] The "deficiency pattern" occasionally seen with hepatic disease may also be related to an abnormal porphyrin content of the blood. Other metabolic diseases which derange motility are thyroid disease,[22] hypoproteinemia,[58] abnormal electrolyte concentrations[57] and azotemia, although the edema which attends a low plasma protein level and the mucosal ulcerations which appear in uremia introduce organic factors in these conditions.

Allergy (see Chapter XLIV) accounts for some of the functional disorders of the small gut, but technical difficulties make the role of hypersensitivity hard to evaluate.

Since the flow of blood and lymph in the small bowel is closely related to intestinal motor activity, functional disorders of absorption as well as of motility are likely to occur. Impaired absorption, as a matter of fact, has been demonstrated in ulcerative colitis[29] and pernicious anemia.[43] Nevertheless, one is justified in emphasizing the abnormalities of motor function, for these are the more readily analyzed by the technics available at present, and they are principally responsible for the symptoms which distress the patient.

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* My observations on emotionally disturbed patients lead me to believe that physiologic alterations in the small intestine play an important role in the body metabolism. The psychodynamic factors causing the physiologic changes have not been sufficiently worked out. Emotional stimulation of the parasympathetic nervous system probably plays the most important part (see Chapter XLIII). Therefore the treatment outlined in Chapter XLIII should be given to a patient who on roentgen study of the small intestine shows the typical pattern emotional disturbance.—Editor.

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CHAPTER XXIII

REGIONAL ILEITIS

In the last ten years a considerable literature has arisen on the topic of regional ileitis. The original description[5] was of a clinical and pathologic entity, really a granulomatous process of chronic inflammatory nature, which occupied, by predilection, the terminal segment or segments of the small intestine.

The disease was characterized by diarrhea and fever, at times by obstructive phenomena and frequently by the formation of fistulous tracts to the abdominal wall or to neighboring viscera.

Nonspecific granulomas of the intestinal tract had been previously described by several observers,[11] but the entire clinical picture of this one subvariety, its roentgen appearance and particularly its surgical treatment had not hitherto been approached.

Many confirmations in the current literature rapidly followed.[1] In particular the surgical fraternity evinced great interest, because with their exploratory operations most of the prominent symptoms of the disease received their earliest appraisal.

It was observed that other segments than the terminal might be involved; in particular, the upper portion and the jejunum.[8] The concept of a combined ileitis and colitis was recognized as a rarer complication of a true terminal ileitis.[2] Other varieties of fistulization were noted, and the surgical profession soon divided into members who advocated simple resection of the pathologic area and those who, for reasons of caution, preferred short-circuiting operations.

To date my experience is based on approximately 200 cases of ileitis or ileojejunitis, in most of which the diagnosis has received confirmation by operation. In the others the clinical course and the reontgen picture have been so characteristic as to defy doubt as to the nature of the process.

Ileitis is not rare; 30 new cases a year in the hands of a single physician cannot be called few. The wide distribution of the cases, in most of the scientific countries of the world, signifies the catholocity of the process. It is not, as has been claimed by some, restricted to Jews; a recent communication indicates it to be widespread in British India, Africa, Sweden, Canada, England and China. In this country, two cases have been reported in Negroes, although in the large Puerto Rican population of New York City I have as yet observed no case.

A definite predominance in the male is indicated, in a proportion of approximately 3 to 2.

However, most of the patients are between twenty and forty. The youngest patient seen was fifteen and the oldest fifty. However, some of the earlier reports emanated from the pediatric services,[14] in which the acute form particularly was seen in young children.

The average age of patients when the disease was first observed or diagnosed was 27.6 years. However, when the history of the individual case is closely scrutinized, it will often be observed that the clinical symptoms date back many years, as much as five to fifteen, so that even in the older patients the origin of the process dates back to the earlier decades. This point is important in diagnosis, for in evaluating supposed ileitis in the later years, one is required to exercise due caution in seeking for other, more common diseases of decrescence, which is less important in the earlier decades.

TABLE 10.—AGE INCIDENCE OF REGIONAL ILEITIS (PERSONALLY OBSERVED CASES) (1940)

Years	Cases
1–10	None
10–20	11
20–30	50
30–40	21
40–50	11
50–60	2

ETIOLOGY

In the compensation courts and civil litigation trauma has been incriminated as a factor in ileitis. Most often some trivial automobile injury without present manifestations of abdominal trauma is followed after a longer (one year) or shorter (three months) period by an operation for ileitis. That some exaggeration of a preëxisting disease or a hemorrhage into such a process may be created is possible. But the unlikelihood of such a relation throws the onus of proof on the one who makes the claim. One case of true traumatic ileitic was, however, encountered. After a severe automobile injury a traumatic duodenal ulcer and a traumatic ileitis were both demonstrated at successive operations. The claims for damages in the courts of law were sustained on both counts.

No true etiologic factor for regional ileitis can be implicated. As for ulcerative colitis, to which ileitis bears some resemblance, a true specific agent remains to be proved. Tuberculosis has been excluded by innumerable cultures, by animal inoculation and by pathologic histology.

The appendix has been accused,[9] but its consistent noninvolvement and the continuation of the disease after its removal (in approximately 33 per cent of my cases) seem logically to absolve it.

Experimentally a picture somewhat like ileitis has been produced by injecting bismuth salts into the lymphatic vessels about the ileocecal junction and following this with an injection of *Bacillus coli,* thus blocking the lymphatic drainage of this sector and producing lymphedema and stasis somewhat analogous to ileitis.[13] The fact that the upper part of the ileum and the jejunum as well as colonic segments are often involved and the recurrence of the disease not infrequently after ileocecal resection seem to nullify a lymphatic origin.

For a disease as unusual as ileitis, it is surprising that I have five times seen more than one member of a family with an identical process. Originally I reported 2 cases in siblings;[3] more recently 2 brothers were subjects of terminal ileitis, and in the recent past I have observed 2 sisters operated on for proved ileitis and a niece, a blood relative, already showing fever, diarrhea and abdominal cramps, although the characteristic *x*-ray picture had not yet appeared. The most likely common infecting agent would be intestinal bacteria, *Shigella dysenteriae,* for example. For years I have been culturing the stools and the resected specimens for dysentery organisms. To date I have had only one successful culture, of a Flexner bacillus; occasional high agglutinations against stock dysentery organisms have been observed (1:320 Hiss and similar fairly high titers), but the etiologic significance of such agglutinations is not acceptable to bacteriologists. Too many group agglutinations occur, and too much cross agglutination is observed to allow an occasional high titer agglutination to be regarded as convincing evidence of the presence of *S. dysenteriae* as the cause of the disease.

Felsen,[6] in an epidemiologic survey, has observed ileitis as well as colitis following epidemic dysentery. In the experience of pathologists and clinicians, involvement of the terminal part of the ileum alone in epidemic dysentery has not been observed, even in wide spread and severe epidemics. However, chronic ulcerative colitis may represent one late phase and chronic regional ileitis another and different late stage of an earlier dysentery manifestation. In the absence of a more significant suggestion as to the etiology, dysentery as a cause, while the evidence is not convincing, deserves further study.

Histologically, ileitis seems to fall into the category of pseudotuberculous diseases. The microscopic picture, as Snapper[15] has shown, is not unlike that of Boeck's sarcoid and similar tubercle-like formations. The finding of tubercle bacilli in any such specimen would, to my view, immediately remove the case from those of ileitis and transfer it to those of the still less frequent forms of primary ileocecal tuberculosis.

PATHOLOGIC DISTRIBUTION

The disease by preference begins at the ileocecal valve and extends upward along the terminal part of the ileum for a variable distance. Most often 8 to 12 inches is involved, with occasionally as little as 2 inches as a minimum and more commonly up to 24, 36 or 50 inches or more. In rarer forms, the whole ileum and lower part of the jejunum may be implicated, and in one case even the duodenum participated in the pathologic process, This is all the more surprising when one notes that the extent of the small intestine is normally 20 to 24 feet.

Only the jejunum and upper part of the ileum may be involved, the whole lower course of the ileum being entirely free of involvement. This is fortunately extremely rare, for it presents a grave problem for surgical therapy.[10] In one case, high jejunoduodenitis with obstruction of the upper jejunum was noted; an intestinal anastomosis surgically performed between the upper part of the jejunum and the third portion of the duodenum resulted in cure.

Succulent, enlarged mesenteric lymph nodes demarcate and signalize the extent of intestinal involvement. They are signal nodes and as such are important landmarks to the examining surgeon as limiting the areas involved. These nodes rarely break down, nor do they become calcified as in tuberculosis. They resemble so much the enlarged nodes of acute mesenteric lymphadenitis seen in infancy that an analogy between the two diseases has often been drawn. It is possible that the latter disease seen at operation in young children is really ileitis with subrecognizable ileal or only mucosal involvement and maximum engorgement of the signalizing mesenteric lymph nodes. This subject will bear close scrutiny. To date in no case has mesenteric lymphadenitis been seen to merge into the clinical picture of chronic regional ileitis, although it might take years for such a transition to occur.

"Skip lesions" are common in regional ileitis. The pathologic process seems to terminate in a variable portion of normal mucosa, to be followed by another area of similar inflammatory involvement of the mucosa and wall of the small gut. The "skip lesions" extend upward for 2 to 12 or more inches—in fact, in one case to 18 inches—and are followed by a short area of diseased intestine. By overlooking and failing to remove such an involved segment, the surgeon almost invariably invites a recurrence of the disease in the higher segments of the small gut, as well as in the colon.

Direct extension to the cecum and ascending colon, as well as "skip lesions" throughout the whole large gut, have been observed in 8 cases. Thus, ileum and cecum or ileum, ascending colon and descending colon may be involved in an interrupted manner. Fortunately for the original concept of a terminal ileitis, these mixed involvements are rare. Often with the resection of the ileum, the colonic involvement may regress; more often, unfortunately, the overlooking of a serious involvement of the colon may lead to secondary recurrent diffuse colitis and recurrence of the ileitis in higher loops of the ileum and jejunum.

SYMPTOMATOLOGY

Occasional cases of acute ileitis are observed by surgeons who, operating under a mistaken impression of acute appendicitis, find it by surprise (11 cases). The symptoms resemble closely those of acute appendicitis, except that almost invariably some history of preceding diarrhea is elicitable. Appendicitis is invariably associated with constipation—rarely, if ever, with loose or frequent movements. The temperature, the rebound tenderness and the mass are common to both diseases. In ileitis the leukocytosis is moderate.

Chronic ileitis usually has a long history, extending over months or years. Usually there have been many years of diarrhea, mild, continuous or in bouts and accompanied by colicky abdominal pain relieved immediately by a bowel movement. Intermittent fever is a frequent though not constant concomitant; some patients are afebrile throughout.

In this series, the anamnesis showed a duration of:

Years	Cases
1– 5	62
5–10	15
10–15 (or more)	8

During the later phases a mass appears in the right lower quadrant of the abdomen or across the suprapubic region; occasionally the mass may be felt even in the left lower abdominal sector or in the left side of the pelvis by digital examination. The mass consists of a soggy, edematous, inflamed terminal portion of the ileum, plus engorged mesentery and adherent neighboring loops of gut. These loops, usually of small intestine or cecum or sigmoid, may become agglomerated to the original ileal mass by fistulous tracts or by localized peritoneal exudates. A slow, walled-off perforation is usually the cause of the localized peritoneal inflammatory mass, which may resemble an appendiceal abscess, a diverticulitis or possibly a secondary ileocecal tuberculosis.

In long-standing ileitis, sufficient scar tissue may remain from successive phases of inflammation to give rise to a cicatrizing process, eventuating in the picture of a low grade or incomplete intestinal obstruction. This was present in 14 cases and was characterized by severe abdominal pain, distention and vomiting, borborygmi and occasionally visible peristalsis.

Occult blood and some mucus are usually present in the stool in ileitis; however, in some low grade varieties repeated examinations of the feces for occult blood may give negative results.

FISTULAS

One of the manifestations of ileitis, if not the most pathognomonic finding, is the formation of many and diverse fistulous tracts, traveling short distances to abdominal wall or neighboring pelvic viscera or long flights to mark their exit at distant points. The fistulas are apparently created by the lytic enzymatic action of intestinal contents released through a slowly penetrating ulceration of the ileum. They usually begin in the mesenteric attachment of the terminal part of the ileum and slowly progress by digestion due to activated ferments. They are rarely highly infectious.

Of these fistulas three main varieties are recognized:

1. **Internal Fistulas (20 Cases).**—These originate in the terminal part of the ileum and end in some other loop of small intestine, the cecum, the ptosed transverse colon or the sigmoid or pelvic colon. The pelvic colon, because of its redundancy, often fills the entire lower part of the abdominal cavity and so lends itself freely to adherence to the inflamed ileum and leads to a fistulous communication. The uterus, ureters, vagina and bladder also occasionally serves as distal exits for ileal fistulous tracts.

2. **External Fistulas (22 Cases).**—These occur distally, most commonly on the anterior abdominal wall and nearly always in the scar tissue of a previous appendectomy. The intact anterior abdominal parietes are never the seat of a fistulous tract, but the usual previous exploratory operation leads most commonly to a persistent fecal fistula in the operative scar.

The inguinal region and the lateral and posterior lumbar walls of the abdominal cavity are occasional exit points of fistulous tracts without previous laparotomy scars. They may form one or more fistulas, usually vertically placed in the right lumbar or perinephric region, emitting thin grumous intestinal contents. Snapper[15] reported the first case of this condition which is rare but confusing.

3. **Perianal, Rectal and Rectovaginal Fistulas[12] (42 Cases).**—These constitute the most common type and are significant in diagnosis. Various type of formation are seen. The majority of perianal fistulas or *fistulae in ano* represent metastatic infection of the crypts of Morgagni, contamination occurring as a result of transported infectious feces. A perianal abscess, as usual, precedes the rupture of the fistulous tract.

Less frequently, however, the tract is a long one, originating in a low-lying intrapelvic loop of infectious ileitis, in which the infected terminal loop occupies its favorite anatomic site on the floor of the true pelvis, over the bladder and the uterus and in the pouch of Douglas. The enzymatic and infectious leak seeps downward through the pelvic peritoneum and fascial planes, seeking, by gravity, an exit. It may perforate into the ampulla of the rectum or, pointing downward, infiltrate through the hammock-like fibers of the levator ani, infect the posterior pelvic triangle and exit about the rectum or into the vagina or both, in the latter case creating a rectovaginal fistula. Or it may, by infecting the ischiorectal fossa, give rise to an abscess and exit on the perineum as a perirectal abscess or fistula.

The course of the tract is often impossible to follow in its continuity. By x-ray the upper origin may be visualized as a streak of barium originating in the pelvic cavity and pointing downward along the rectum. By lipiodol injection into the distal end, or exit, the course may be followed upward toward the pool of barium seen in the perirectal spaces. The complete continuity of the tract may be difficult to establish, but the foregoing explanation is offered as the most plausible and logical one to account for the sequence of events.

Perirectal or anal fistulas may precede by years the onset of the true characteristic symptoms of ileitis, particularly the diarrhea; they constitute the one prodromal sign of terminal ileitis. In every case of *fistula in ano* a complete history should cover the presence or absence of diarrhea. If diarrhea is present, complicated by a fistulous tract, ileitis should be sought for. Of course, ulcerative colitis may produce the same picture, but a normal sigmoidoscopic picture throws the diagnosis back to the more probable ileitis.

COURSE AND PROGNOSIS

Acute Ileitis.—Most lesions of this type seen at operation are not resected. The after history is variable. Undoubtedly many of them undergo recession with healing. The transition between acute ileitis and chronic regional ileitis has rarely been observed. In one patient, who did not undergo exploratory operation, subacute ileitis was followed for two and one-half years, during which time the complete picture of a chronic terminal ileitis developed. Of 11 patients with acute ileitis, 8 did poorly, eventually coming to operation. In the other 3 the condition subsided; to date these have remained well.

Chronic Ileitis.—Unoperated on, this form has a variable but as a rule unfavorable course. Over many years the diarrhea becomes a major factor, and nutritional disturbances and an avitaminosis may develop, complicating the occurrence of multiple fistulous tracts.[4]

In 2 cases death was due to localized perforations with low grade suppurative peritonitis, determined by autopsy. Intra-abdominal abscesses, localized peritonitis and fistulas to the colon, bladder and abdominal wall created the fatal issue in these cases.

DIFFERENTIAL DIAGNOSIS

Given a protracted diarrhea in a young person, a mass in the lower right quadrant of the abdomen, fever, anemia and a typical radiographic picture of a filling defect in the terminal part of the ileum, the diagnosis of ileitis should not be difficult. It is absurd to say that ileitis cannot be diagnosed before exploratory laparotomy. The normal sigmoidoscopic picture rules out ulcerative colitis; the barium enema confirms the absence of colitis, but may indicate some segmental involvement of the ascending colon, with an associated terminal ileitis. It is very important at all times to determine whether ileitis alone or a combination of ileitis and colitis exists, for the surgical approaches are different.

Roentgenologically, both the barium enema and the barium meal are available for the discovery of ileitis. The enema has the advantage of determining whether the colon is involved; the meal gives better differentiation of the terminal portion of the ileum, particularly where hourly fluoroscopic observations are made and frequent plates taken. The characteristic "string sign" is almost pathognomonic. Rarely, however, the *x*-ray picture is normal; this fact should not, to my mind, exclude a clinical diagnosis of ileitis, nor should an exploratory operation be withheld because of the lack of roentgen confirmation of a logical diagnosis. It is essential, however, to rule out a thyrogenous diarrhea by a basal metabolism estimation and to exclude a gastrogenous diarrhea by the use of a test meal. Nervous and emotional diarrheas, as well as gastrointestinal allergy, deserve, in the same manner, due consideration.

In nontropical sprue, the "puddling" and delays in the high jejunal loops are rare, while in ileojejunitis consistent filling defects are frequently seen. The stool of sprue is characteristically frothy and abundant; that of ileitis is watery and contains pus and occasionally blood grossly or chemically. The anemia of ileitis is rarely severe and never of the hyperchromic type seen more regularly in sprue. In ileitis the terminal part of the ileum is, if not the primary seat of the disease, nearly always involved, a fact which does not pertain in sprue.

Hodgkin's disease and multiple primary sarcomatosis of the small intestine are extremely rare in comparison with ileitis. They both give rise to rapid emaciation and gross hemorrhage and run a more severe and quickly progressive and fatal course. Ileitis is a long drawn out mild process in comparison with either sarcomatosis or Hodgkin's disease.

Primary ileocecal tuberculosis also is rare in comparison with ileitis. In a complete pathologic survey of all the autopsy and surgical material at the Mount Sinai Hospital for sixteen years, in only 8 cases was true primary ileocecal tuberculosis proved. In 2 of these cases the terminal part of the ileum was the seat of a true primary mucosal tuberculosis; in 6 other cases the ileum and cecum were involved. In all other cases the supposed primary intestinal tuberculosis was secondary to a process elsewhere in the body, namely, in the lungs, joints or lymphatic apparatus.

TREATMENT

A specific conservative or medical approach does not exist; the long, slowly downward course cannot be interfered with or changed by any method now known. Vaccines and specific and nonspecific protein therapy have not been of any avail.

When the patient refuses operation, or when diffuse involvement of the whole ileum and some of the jejunum indicates the massive resection with its attendant risk, one must adopt some nonsurgical plan of supportive therapy. This should consist of giving a nonroughage diet, opium for the diarrhea and iron for the anemia and vitamin replacement. Occasionally patients with diffuse ileojejunitis do well under such conservative therapy. One patient gained 50 pounds; however, subsequent *x*-ray study revealed the persistence of the lesion, though undoubtedly some healing and scarring of the intestinal mucosa did take place. That healing can occur is proved by the cases in which late obstructive symptoms in the intestinal lumen are due to scarring and cicatrization.

The treatment of choice in ileitis is surgical, preferably, when possible without undue risk, resection of the involved segments of small intestine. Whenever the terminal part of the ileum is the seat of the disease, the resection should include all of that part and the "skip lesions," including those of the cecum and ascending colon, as ileotransversostomy can be safely performed with a low risk and a good functional result. No attempt should ever be made to resect a segment of the terminal part of the ileum and reimplant the ileum into the ileocecal valve, an error which quickly results in relapse and recurrence at the site of the anastomosis.

The surgical risk of localized resection of the ileum and cecum is about 15 per cent; the result is usually good.

Many surgeons today prefer a short-circuiting operation, usually in the nature of an ileo-transverse-colostomy or an ileosigmoidostomy. In a recent paper, Ginzburg and Garlock[7] reported 54 cases of ileitis treated by conservative short circuiting, without surgical mortality. Not only is such an operation much safer, but the authors claimed—on good grounds—that healing can and does take place in the short-circuited diseased segment. This claim they based on two facts: 1. Subsequent laparotomy demonstrated extensive regression of the pathologic process, disappearance of the mass and evident scar tissue formation. 2. The by-passed fecal fistula to the abdominal wall and adjacent viscera almost invariably disappeared. Of the 54 cases in which ileocolostomy with exclusion was done, there was recurrence of the disease or persistence of the process in the proximal loop in 5. Unfortunately, one can no longer deny the possibility of recurrence after either radical resection or more conservative short-circuiting operations. The percentage of cases of recurrence proximal to the new anastomosis is probably high, even though the resection or anastomosis is made high in the ileum and all diseased areas and "skip lesions" are excluded. Such recurrence is best explained on the basis of a greater mucosal involvement than was visible on roentgen examination or palpable to the hand of the surgeon at the time of laparotomy. It is possible also that the regional lymph nodes in the adjoining mesentery serve as a nidus of reinfection.

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CHAPTER XXIV

INTESTINAL TUBERCULOSIS

DEFINITION AND ETIOLOGY

Tuberculosis of the intestine is most properly classified as primary, or hypertrophic, and secondary, or ulcerative. The secondary type, which is of major importance, is tuberculous ulcerative disease, occurring in the small or large bowel, and practically always in association with healed or active tuberculous disease in the lungs. The primary type, conversely, is very uncommon in conjunction with an active pulmonary lesion.

In secondary intestinal tuberculosis which is associated with pulmonary tuberculosis, direct responsibility for infection in the intestine rests solely on the lung condition. There is little doubt that, except in the rare cases in which it may occur by blood stream invasion, infection is the direct result of a constant passage of tubercle bacilli, usually large, derived from the sputum that is swallowed, and the continued passage of tubercle bacilli contributes to the greater improbability of healing and to extension of disease in the bowel greater than if the passage were not continuous. This is well borne out by published statistics showing the high incidence of tuberculous disease of the bowel with far-advanced pulmonary disease, that is, in the presence over a period of time of cavitation in the lung and much sputum. With rare exceptions, tuberculous enterocolitis may be said to be a lymph-borne disease.

Intestinal ulceration is present much more frequently in the presence than in the absence of pulmonary ulceration. Clinical experience, as well as autopsy findings, indicates that laryngeal tuberculosis, as well as intestinal tuberculosis, is most commonly a sign of far-advanced disease or of disease associated with the raising of a quantity of tuberculous sputum. Rubin,[20] in a correlative study involving 569 autopsies of tuberculous patients, found 1 out of 2 had laryngeal involvement and 2 out of 3 had intestinal involvement. He found that of the group with trouble in the larynx, 90 per cent had intestinal involvement. Laryngeal and intestinal involvement coexisted in 39 per cent of all cases, and neither was present in 30 per cent.

Since sputum is continually swallowed inadvertently or otherwise by the tuberculous patient, tubercle bacilli may always be found in stomach washings of bacillus-positive patients and in practice are frequently found even when expectoration shows no organisms. Tubercle bacilli, then, are constantly being passed through the gastrointestinal tract, and their constant presence there is responsible for infection in this area. Other factors which directly contribute to infection in the intestinal tract are not well known, but cecal stasis, suboptimal nutrition and vitamin deficiencies are to be considered.

PATHOLOGY

Intestinal ulceration is by far the commonest complication of pulmonary tuberculosis. The most reliable figures available indicate that at autopsy 50 to 80 per cent of the patients dying of pulmonary tuberculosis have ulceration of the bowel. The longer the duration and the greater the involvement of the lungs, the more sure the intestine is to show ulceration. The ulcerative type may be divided into the common secondary ulcerative type which complicates pulmonary tuberculosis and a type, exceedingly rare except in children, in which the intestinal lesion is the primary one. We have recently seen evidence of this rare type in an adult who had severe intestinal less ulceration, presumably the result of ingestion of tubercle bacilli by kissing. The bowel ulceration appeared first, and later a lesion appeared in the base of one lung. There was no expectoration at any time.

Tuberculosis of the intestine may occur at any age, but is more commonly observed between the ages of twenty and forty, although it occurs not infrequently in children. The sexes are equally affected.

Necropsy Incidence

Author	Cases of pulmonary tuberculosis	Percentage of intestinal tuberculosis
Zahn[27]	1,528	63.2
Crawford and Sawyer[8]	966	66.8
Engelsman[10]	108	92.6
Fenwick and Dodwell[12]	200	56.6
Steinbach[22]	199	65.3
Radiologic Incidence		
Steinbach[22]	127	38.6
Brown, Sampson and Hayes[5]	1,036	31.0
Granet[13]	2,086	38.35
Williams[26]	1,088	18.93

Blumberg[1] stated that roentgen recognition of intestinal tuberculosis occurs with 5 to 8 per cent of early, 14 to 18 per cent of moderately advanced and 70 to 80 per cent of far-advanced lung disease.

The exact pathogenesis is not yet proved, because of the difficulty of producing tuberculous ulceration in the bowel of small animals used for experiment. It appears probable, nevertheless, that the infection is enterogenous rather than, as some authors have stated, hematogenous. The difficulty of experimentation is exemplified by the work of Medlar and Sasano,[19] who inoculated 8 guinea pigs subcutaneously. Of these, one showed typical ulcers in the bowel, but the others showed no gross lesions. Serial sections of lymphoid tissue from the bowel, however, manifested tuberculous lesions and tubercle bacilli in every case investigated. The initial lesion appeared to be an inflammatory exudate in the intestinal glands, which entered deepest into the lymphoid tissue. From here the bacilli were carried through the surface epithelium, setting up lesions in the underlying submucosa without ulceration.

It is obvious, therefore, that the epithelium over the ulcerative lesions in some cases may become necrosed and be cast off, leaving an ulcer, whereas in other cases it may remain intact, leaving the lesion not grossly discernible. The mesenteric lymph nodes are always infected. Therefore it is evident that the initial lesion in the bowel wall may become ulcerated or not and that lesions in the lymph nodes indicate the presence of lesions in the bowel wall, although these may not be visible to the naked eye. It should also be remembered that when an animal is inoculated subcutaneously the liver usually becomes invaded with small lesions, which rupture into the bile ducts and thereby open another avenue of infection for the intestine.

At autopsy the ulcerative lesions may be scattered over a wide area, but operative work and x-ray study have shown that the earlier lesions are in the ileocecal region, whence the infection spreads upward and downward in the bowel. A localized lesion may be found in the stomach, duodenum, jejunum, upper part of the ileum or terminal half of the colon. These sites are usually involved when extensive disease is present in the more commonly affected segments. The universal affinity of tuberculous infection for lymphoid tissue is again manifest because the ileocecal region is most richly supplied with it. The earliest lesions are seen in Peyer's patches and the solitary lymph follicles. They are gray and translucent at first but later become caseated and yellowish. The mucosa lying over the focus is injected and swollen, and after its destruction a shallow ulcer with ragged, undermined edges is present. The base of the ulcer may be in the submucosa or the muscularis or directly on the serosa. In general, because lymphatic drainage runs around the bowel, the ulcer tends to encircle the bowel, although longitudinal ulcers are not uncommon. Ulcers may vary greatly in size. The process of ulceration is comparatively slow, so adhesions to adjacent tissue outside the bowel are common and account for the low incidence of perforation.

Microscopically, caseation is prominent, along with endothelial cell and lymphatic infiltration and giant cell formation. The walls of the smaller arteries are thickened and their lumens narrowed, often to the point of obliteration. This endarteritis obliterans explains the infrequency of the complication of hemorrhage.

Healing of the intestinal ulcers is known to occur. Granulation tissue forms in the base and through the submucosa, and the mucosa may be completely renewed. Healing may be found in some ulcers while others are progressing or while pulmonary activity is still present. When the bowel lesions are extensive and healing takes place, cicatricial tissue is formed and obstruction of varying degree results, particularly when the ulcer is of the usual encircling type. This type of obstruction is not so common as a result of tuberculous ulceration as is the type which comes from partial perforation and the consequent adhesions and kinks. Obstruction resulting from either cicatricial narrowing or adhesions is the most common complication, and is difficult to deal with surgically.

Peritonitis is often encountered in late disease, and fistula formation is a common complication following surgical measures.

SYMPTOMATOLOGY

The symptoms of secondary tuberculous intestinal disease are varied and may be readily confused with symptoms of other gastrointestinal disorders. The severity of symptoms in no way parallels the course of the disease, except in its far-advanced stage, and the diagnosis of intestinal involvement may be made more certainly by considering the type of lung disease than by relying on the dyspepsia syndrome presented. Medical men are often led to treat digestive symptoms as digestive disease when these symptoms are really only the result of toxicity from a lung lesion. These toxic symptoms manifest in the digestive tract are frequently more pronounced that when the disease is actually present in the bowel. It behooves one, then, who is searching for the cause of bizarre digestive complaints often felt to be of psychogenic origin to examine the chest diligently, and stethoscopic examination gives no final word as to the presence or absence of pulmonary tuberculosis. Roentgenograms of the chest must be made, and any sputum examined for tubercle bacilli.

The human digestive tract is generally recognized as being responsive in an almost predictable way to toxic, emotional and fatigue states. The dysfunction of alimentation seen with tuberculous disease of the lung is a typical example. Observation of many cases has led us to believe that this is a combined toxic and fatigue effect. Fatigue, so often present when the patient is ambulant, results in many gastrointestinal symptoms, which disappear when bed rest is accomplished. The anorexia, which may be almost severe enough to be nausea, is often most marked in the morning. Breakfast may be confined to only a little liquid nourishment. Food intake for the day is below the basal need, and loss of weight results. Gaseous or acid eructation, abdominal distention, pain and discomfort after eating are common. Bowel function becomes upset because of lowered food intake and a spastic state, and the condition often is treated as "colitis" or irritable colon. These manifestations call for rather complete investigation. The gastrointestinal manifestations of pulmonary tuberculosis are fundamental—always taught but often overlooked at the appropriate time. Every year numerous patients come to Arizona for the treatment of pulmonary tuberculosis in all stages, and the history taking is a revelation of the failure of physicians who are not tuberculosis conscious to apply the knowledge that gastrointestinal symptoms are often the first and only signs of pulmonary tuberculosis. It is well to be tuberculosis conscious when considering obscure gastrointestinal symptoms and to have an x-ray picture of the lungs, since the surest method for prevention of intestinal tuberculosis is the early determination and treatment of the pulmonary lesion. Gastrointestinal symptoms as often indicative of infection by Koch's bacillus in the lung cannot be too much emphasized.

The rather common conception of tuberculous ulcerative colitis as having marked and severe symptoms is not tenable. Rather extensive disease may give severe symptoms or, on the other hand, none at all. Many patients at autopsy show ulceration, previously unsuspected, to be extensive. Disease of slight extent may give severe symptoms or may give symptoms of only passing importance, the severity of which is no more than is expected with the toxemia previously mentioned as accompanying the pulmonary condition. The symptoms are in great part not possible of correlation with the extent of bowel involvement, and to say that a patient does or does not have tuberculous disease of the bowel on the basis of symptoms alone is to risk the possibility of error. Functional gastrointestinal derangements often associated with pulmonary tuberculosis may present all the characteristics of intestinal tuberculous involvement when it is in reality absent. Nontuberculous organic conditions occur in the tuberculous as well as in other patients and frequently present problems in diagnosis.

Because of the indefiniteness of the symptoms, even mild abdominal complaints should be looked on with suspicion in the tuberculous and especially in patients with ulcerous disease in the lung or with bacillus-laden sputum. *Irregularity of temperature or temperature unexplained by the lung condition, sudden reversal of form in a patient's previously good* *course or continued unsatisfactory progress should immediately suggest bowel involvement.* Unexplained nervous irritability, gaseous eructation, distention after eating, borborygmus, loss of appetite, nausea, vomiting and constipation or an occasional loose stool are all indicative enough to demand further examination. These symptoms in themselves are inconclusive, but must be taken into account in the final analysis. Erickson[11] said: "The symptomatology of intestinal tuberculosis is most varied. It is impossible to make out any one diagnostic syndrome or any one sequence of symptoms; the various symptoms occur and follow each other in a manifold variety."

Pain is probably the most common symptom but, like other symptoms in this disease, is inconstant and often not proportional to the extent or duration of involvement of the bowel. The pain complained of is usually located in the right lower or middle portion of the abdomen. It may vary from the most frequent kind, which is of a dull, aching or burning nature, to severe cramplike or sharp and lancinating pain requiring opiate medication for relief. The crampy pain makes the patient afraid to eat, since it is induced by putting food into the stomach, and attention is therefore directed to the stomach rather than the intestine. When food enters the empty stomach, the gastrocolic reflex induces peristalsis in the colon, and the gastroiliac reflex tends to relax the ileocecal valve. Thus, such a stimulus as the presence of food in the stomach produces muscular activity in the involved area and gives the response of pain or discomfort. *Determination of the origin of pain induced by eating is an important diagnostic item.* It is generally recognized that functional digestive disorders produce pain and discomfort on eating in a like manner, but careful analysis shows that the pain or discomfort accompanying these conditions is not so constantly in the same location, nor does it occur so regularly, as with tuberculous enteritis. Pain may also be produced by deep-seated disease in the bowel wall and involving the peritoneum. Deep ulcers which penetrate mucosa, submucosa and muscularis set up a peritoneal irritation which excites the most persistent pain to be dealt with. This process is regularly associated with nausea, vomiting and rise in temperature. Acute involvement of the mesenteric glands produces excruciating pain. Palpation over the diseased area often elicits pain when otherwise it is not present. Repeated finding of a tender area in the same location, especially if the bowel is palpably thickened, is strong evidence favoring intestinal infection.

Intestinal tuberculosis is not always accompanied by diarrhea. Usually when diarrhea is present continually, ulceration is extensive. An occasional loose stool or recurrent diarrhea is nevertheless one of the most common major symptoms. Although constipation is frequently complained of in the whole group of cases encountered, it is not sound to accept the patient's statement that he is constipated, since with many patients constipation is not real but imagined. It is actually present in about 30 per cent. Diarrhea is no more a true index of ulceration than constipation is an index of its absence. Inflammatory changes in the intestinal wall without ulceration often produce bowel looseness. Disturbances in bowel function coming repeatedly and becoming more frequent and more severe or a change in bowel function from a previous rather constant status is suspicious evidence of intestinal involvement. The patient is likely to be upset by small indiscretions in diet which previously did not bother him. Rough or raw foods or cold liquids begin to disagree with him. The discomfort and alteration of bowel function after indiscretions are apt to become worse or at least to recur persistently.

In the severe diarrhea accompanied by much pain requiring opiates in the presence of extensive involvement or when the rectum or lower part of the colon is involved, the stools are copious, watery and foul smelling. They contain pus and blood. The colon is intolerant to the fecal content, which is hurried through without absorption of water.

Hemorrhage from intestinal tuberculosis is rare in our experience, although death has been reported from it. Anemia is frequently found when the intestine is involved, but it is not certain whether it is partly of toxic origin or entirely the result of invisible blood loss. Blood loss of macroscopic extent is certainly not common.

The temperature curve is typical of the bizarre situation throughout. Its irregularity is the remarkable feature, as contrasted with the more regular curve seen with uncomplicated pulmonary disease. The highest recorded temperature for the day may occur at 11 A.M., or the early morning subnormal value may persist throughout the forenoon. Often the high point of the day may be at 8 P.M. The temperature may remain normal for several days and then go to 99.2 to 99.6 F. This occurs particularly when the patient has eaten indiscreetly. Frequent digestive upsets accompanied by a small increase in temperature and variation in bowel function are almost pathognomonic of bowel involvement. More pronounced reactions are most reasonably connected with food poisoning or food allergy. The temperature may not be affected at all by tuberculous enterocolitis, or it may present the diagnostic irregular irregularity.

Loss of weight is marked when accompanied by anorexia and many of the other symptoms so common to the disease. In practically all cases nutrition suffers. It may only become manifest, and commonly does, by a failure of the patient to gain weight even though the food intake seems adequate. In all cases, of course, motility of the bowel is disturbed; thus absorption is interfered with, and malnutrition results.

DIAGNOSIS

The diagnosis of tuberculous enterocolitis is difficult clinically except in the presence of far-advanced pulmonary disease with marked bowel symptoms and often a tuberculous larynx. The same symptoms may be present both with and without intestinal involvement.[11] However, the incidence of an individual symptom, such as pain, is greater in the presence than in the absence of such disease. This, unfortunately, is of little help in considering an individual case. It has been repeatedly proved that a diagnosis based on symptoms alone is attended with great inaccuracy, both in missing actual involvement and in diagnosing intestinal trouble later proved absent at autopsy.

The symptoms and physical signs involved should help more in arriving at the correct diagnosis by suggesting x-ray investigation than in any other way. *Symptomatology is helpful but not diagnostic.*

Clinical laboratory methods are of practically no help in the diagnosis. Volumes have been written pro and con, and a tremendous amount of experimental work has been done on the finding of tubercle bacilli in the feces. The accepted opinion has more and more come to be that tubercle bacilli found in the feces are from swallowed sputum. No authority attaches any importance to their presence as a diagnostic aid in the determination of tuberculosis of the bowel.

The finding of macroscopic blood in stools is uncommon. Benzidine tests of stools of patients on a meat-free diet are of little help, because tuberculous ulceration may be present without the presence of even occult blood. Ulceration occurs in the lungs of many patients for years without macroscopic blood being found in the sputum, and the tuberculous process in the bowel may likewise produce no macroscopic blood.

Pus is often found in small quantities from time to time but is an inconstant finding except in far-advanced disease.

The blood findings are of no diagnostic help.

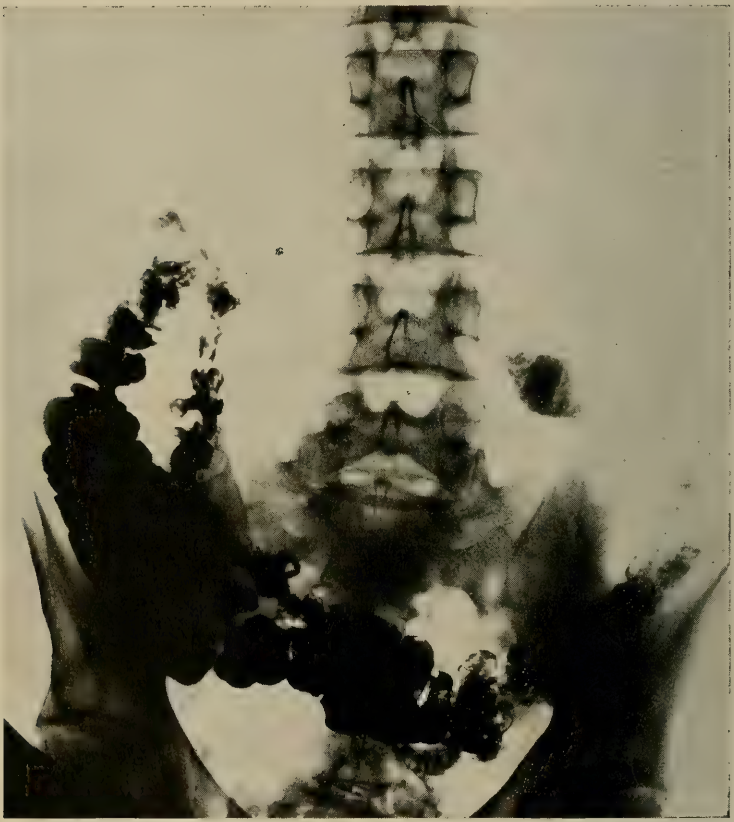

Fig. 100.—A ninth hour film, showing barium retained in the abnormal terminal portion of the ileum. The whole right half of the colon reveals evidence of ulceration.

The Triboulet test (for soluble albumin in the feces) has been put forth by some authors as diagnostic, but it is not specific for ulceration in the intestine.

X-RAY DIAGNOSIS

Roentgen examination is the most important and the deciding factor in the determination of tuberculous involvement in the intestine. Stierlin[23] in 1911 first noted the value of motility studies. The ulceration in tuberculosis is no different roentgenologically from ulceration of other types. Extensive ulceration is easy of diagnosis. Lesser or minimal ulceration must be diagnosed on the basis of a type of evidence little used in other fields. Brown and Sampson[4] have put this type of x-ray investigation on a sound basis, and little has been added to their method.

The method is based on variations in motility, which may be broadly classified as hypomotility and hypermotility through certain segments of the intestinal tract, and on filling defects. Other points are considered, but these signs of indirect and direct nature are the ones of major importance. The filling defects are usually spastic and may not be found by enema. They are nevertheless significant of ulceration.

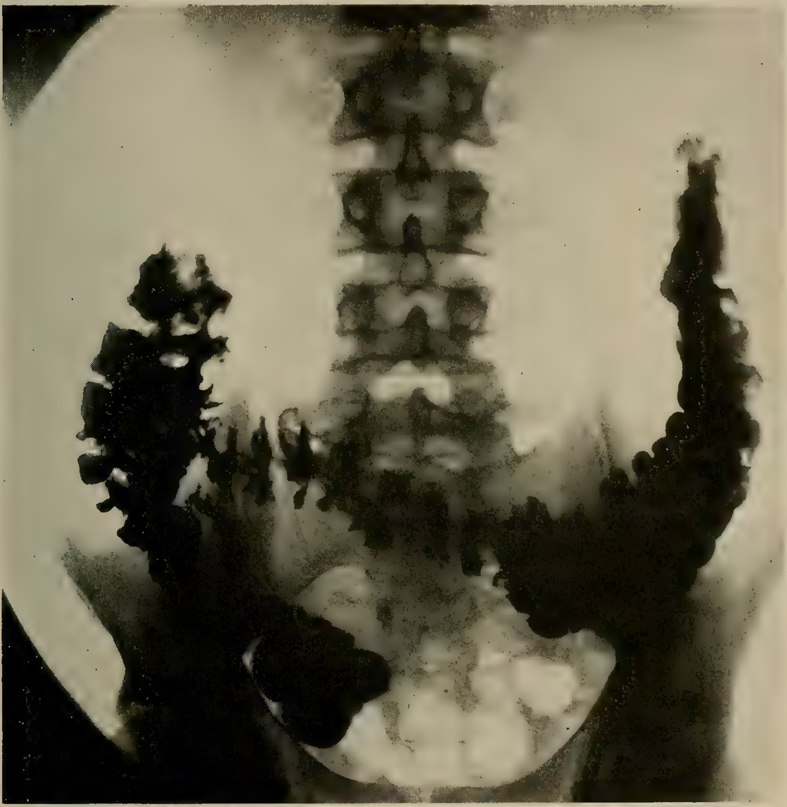

FIG. 101.—Marked motility changes and filling defects seen in a sixth hour film. Ulceration is extensive.

The examination should be made when the subject's intestinal tract is not influenced by laxatives or by food, except the food taken with the barium meal. Variations in routine are used by different authorities, but the essential part is visualization from the sixth or seventh hour through the ninth hour and again at the twenty-fourth hour, followed the same day or at a later date by a barium enema. The barium enema may not be needed for arriving at a diagnosis. A satisfactory method is to give 4 ounces of plain barium mixture with the usual breakfast at from 5 to

7 A.M. and to have the patient report at the x-ray department two to five hours after this. There is little advantage in examination before five hours has elapsed, but occasional involvement high in the bowel or rapid emptying of the stomach may be recognized if observations is made early. If it is also desired to examine the stomach, the barium meal is administered with the stomach empty at the fluoroscopy table. Hourly study of the progress of the meal, when possible, is greatly helpful in gaining more concise ideas of upper intestinal motility and in studying gastric emptying in relation not only to tuberculosis but to other diseases. In the small bowel dilatation and segmentation are the indirect signs of an ulcerative process. The barium is slowed up proximal to the affected area because of spasm, and such delay may persist for an hour or as long as eight hours. If observation is not made before the seventh hour, the abnormality may be missed. Retentions in the small intestine should not be confused with diverticula, which are more common than is recognized. Through x-ray study of the small intestine, heretofore much neglected, the poor status of medical knowledge of this matter, in the past calmly accepted, could be

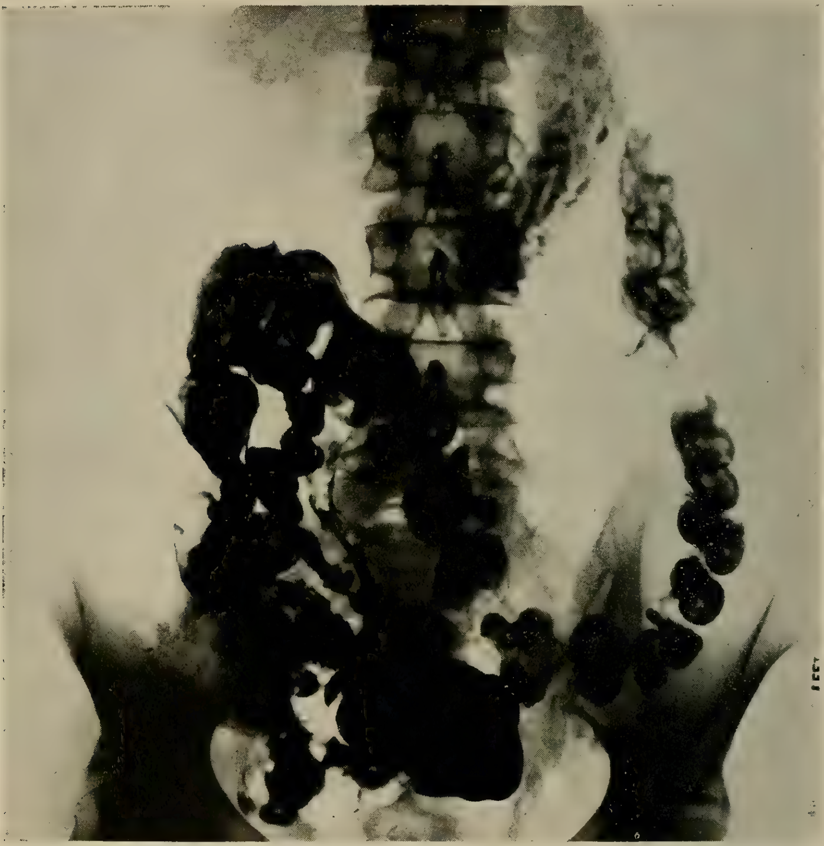

FIG. 102.—A ninth hour film, showing gastric retention. Much barium has passed through a poorly filled cecum and ascending colon, and barium is also seen in the defective small bowel.

improved. It is not only probable but almost certain that if extensive study of the small intestine were made, a code of normal and abnormal could be established which would prove of great benefit.

From the fifth to the ninth hour barium lies in, and is being passed through, the terminal part of the ileum and cecum. Here are the most frequent sites of disease, and most careful observation is necessary. Fluoroscopy is helpful in distinguishing fixation, tenderness and thickening, but films are essential for record, comparison and true evaluation. The exact time that films should be taken is not fixed and definite. They should be made at the optimum time, which is determined by previous films made in the same case, with consideration of the location of barium. Films should always be made at the eighth or ninth hour. A twelfth hour film is often helpful.

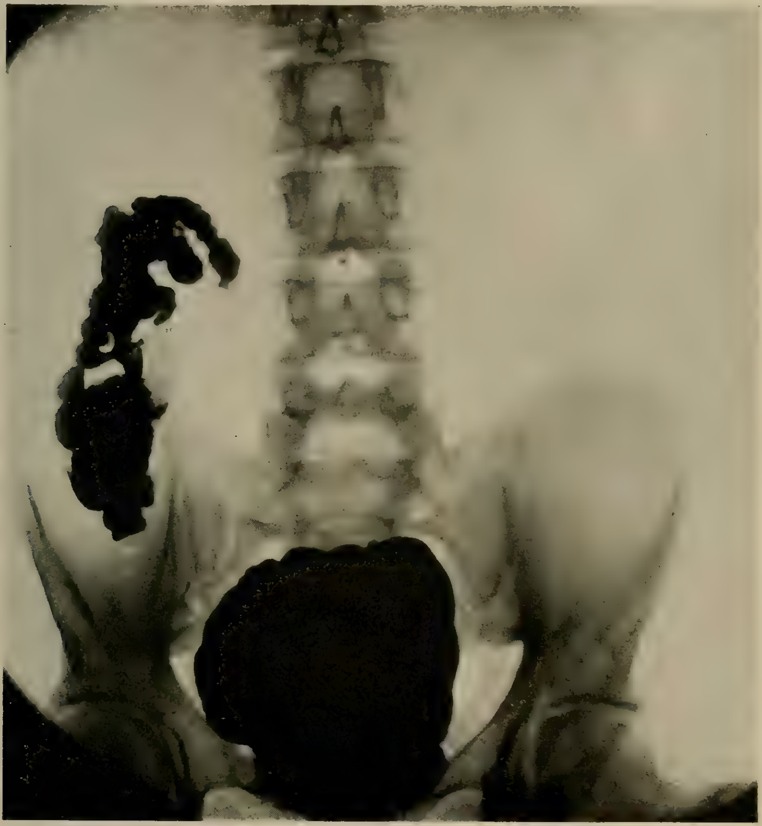

FIG. 103.—Ninth hour film, showing most of the barium lying in the rectum with the cecum poorly filled.

The bowel should not be disturbed by laxative or enema until a twenty-four hour observation has been made. It is practicable to administer the enema also at the end of this twenty-four hour period, since it has not been found necessary or desirable to cleanse the bowel completely in preparation. The barium enema is always administered under fluoroscopic control. Retrograde filling of the ileum often gives invaluable information on the status of this segment. A film made after expulsion of the enema is helpful. Boles and Gershon-Cohen[2] strongly favored the double contrast enema, which includes the insufflation of air into the intestinal tract in conjunction with barium as a help in the diagnosis. It is of unquestioned aid in many instances, but we feel that its routine use is hardly advisable.

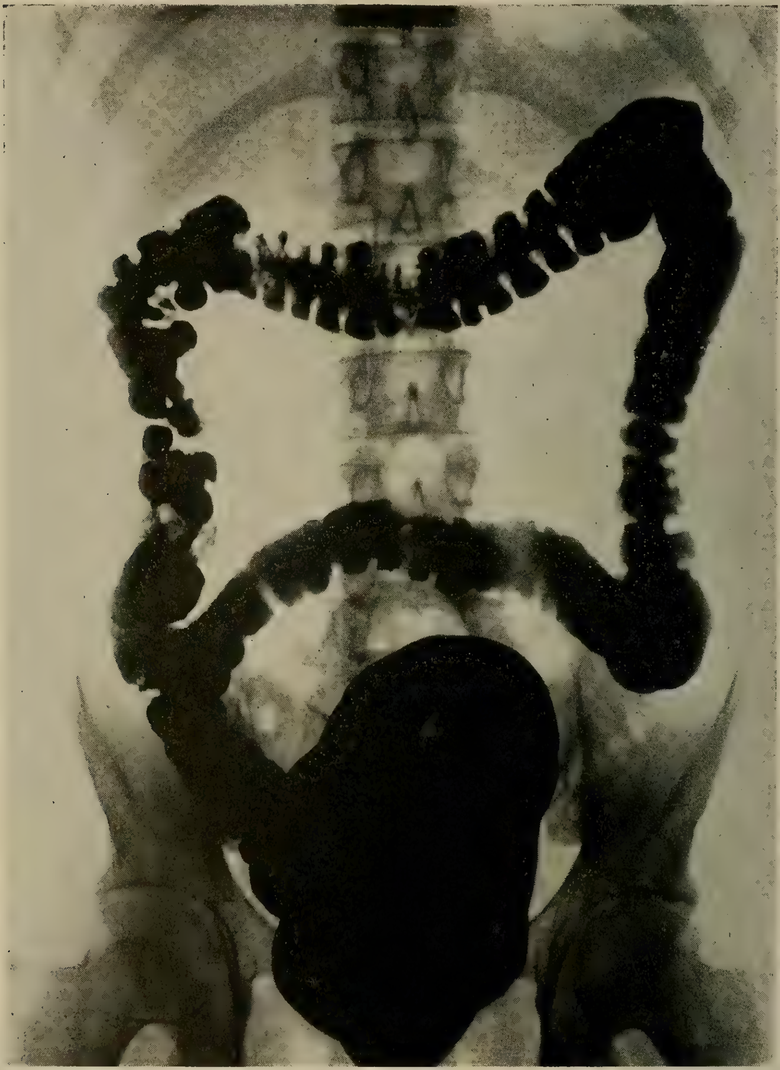

Fig. 104.—A colon enema shows spastic defects from the cecum to the midtransverse part.

The *x*-ray study of tuberculous patients is necessarily a rather laborious procedure for both the examiner and the patient, particularly when the patient is quite ill, as so many of them are. Observation made from the seventh to the ninth hour combined with twenty-fourth hour observation and the barium enema will usually give all the information necessary.

Methods applicable to *x*-ray examination for other diseases of the gastrointestinal tract are not entirely the methods used here, that is, one does not search to find an ulcer but one does search to find indirect evidence of the ulceration. Ulcers can be demonstrated, but the consequent delay would result in missing most of the early positive evidence. The *x*-ray study is primarily a study of motility and of filling defects.

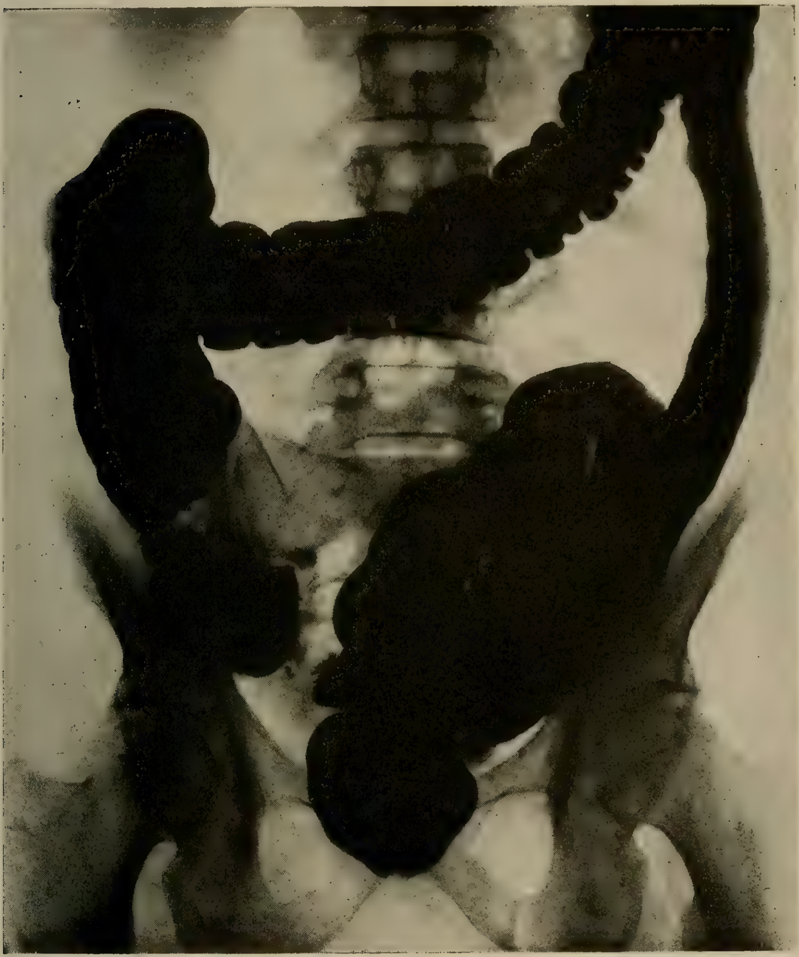

FIG. 105.—A colon enema shows a marked spastic defect in the ileocecal region.

The filling defects here spoken of are not usually, though they may be, the result of fixation of the bowel wall in the position noted, but are due to increased irritability and spasm at the site of the mucosal change. Such states of mucosal tuberculosis cause altered motility. The opaque medium is retarded proximal to the lesion, hastens through the area of the lesion and, when seen in this area, shows filling defects. Enough barium must have passed through the suspicious area to have filled it had the barium been retained. Many such defects are entirely erased if the barium enema alone is depended on.

Normal motility from stomach to rectum varies greatly. Barium goes rapidly through the jejunum and less rapidly through the ileum; normally it enters the cecum in from two to five hours. Ileal stasis, usually indicating ileocecal or cecal involvement, may be diagnosed if the barium lies piled up in the terminal part of the ileum and none has entered the cecum after six hours. Any barium remaining in the terminal part of the ileum after nine hours may also be considered indicative of ileocecal or cecal disease. Furthermore, the cecum should remain well filled out from the sixth through the twelfth hour. Failure in this means disordered motility. If barium remains in the ileum, the ascending colon is well filled and the cecum is poorly filled at any time, disease is present in the cecum. The application of this principle, that a poorly filled area noted serially when barium fills the lumen well on either side, gives diagnostic evidence up to the midportion of the transverse colon. From this point on the barium column may normally not be intact. Proximal to this point, the large bowel should be well visualized, and there should be no defect from the head to the tail of the barium column. Passage of the barium to the terminal part of the colon in the first twelve hours or elimination of most of the barium from the colon in the first twenty-four hours is pathognomonic when unexplained on any other basis. Gastric retention after six hours when associated with motility changes in other segments is often found in the presence of tuberculous involvement. When the meal is first taken, the stomach may empty rapidly, but when the head of the meal reaches the diseased segment, emptying of the stomach is slowed up.

Brown and Sampson[4] studied 5,542 patients with the roentgen ray subsequent to 1918, for the purpose of determining the presence or absence of intestinal tuberculosis. The number of positive results was 1,465; the number of negative results, 4,077. Of the group giving negative results, 88 went to autopsy. In 87 no intestinal tuberculosis was found. Brown and Sampson and most other workers have accepted the method involving x-ray examination as highly satisfactory. Their operative and postmortem findings on patients who have been examined support its efficacy.

DIFFERENTIAL DIAGNOSIS

Carcinoma of the Colon.—Carcinoma of the colon occurring in the tuberculous patient may be confused clinically with tuberculosis of the intestine. It occurs more frequently in later life, while tuberculosis more often occurs in the third or fourth decade. The x-ray diagnosis may be difficult with certain types of tumor about the right side of the colon. A scirrhous lesion may be particularly troublesome. Motility changes are not so important in carcinoma, except when an obstruction exists. The effect on adjacent areas of the bowel is slight, because the tissue change is more localized than that accompanying tuberculous enteritis. The barium enema distinguishes carcinoma most readily. An obstructive tendency is much more definite in carcinoma than in tuberculosis of the bowel. The differentiation of hypertrophic tuberculosis of the bowel and carcinoma is not possible except by exploration. The differentiation of ulcerative tuberculosis of the bowel and carcinoma is not possible clinically but should be readily made in a majority of cases by x-ray examination.

Amebiasis.—Amebiasis produces symptoms and changes in the bowel which may be difficult to differentiate. The finding of amebas by examination of fresh warm stools or by cultural methods proves the diagnosis of amebiasis but does not disprove that of tuberculosis. They can exist together and produce troublesome symptoms which are extremely resistant to treatment. When dysentery is present with amebiasis, blood and pus are present in larger quantity than in the presence of tuberculous ulceration. As in carcinoma, the *x*-ray differentiates best with the barium enema. In amebiasis, when *x*-ray changes are present the bowel loses its haustrations, becomes smooth and shows smooth tapering irregularities in caliber, as contrasted to the rough irregularities and spastic defects seen in the tuberculous bowel. The final conclusion sometimes must be deferred until possible amebic changes have been eliminated by treatment.

Regional Enteritis.—Regional enteritis, which is now being more commonly recognized, is difficult to differentiate when it occurs in the tuberculous patient. Clinically, although tumor formation is more likely with regional enteritis, it is also often found in the tuberculous bowel. Both lesions have a predilection for the same segments of intestine, that is, the ileum and right side of the colon. There are many points of similarity roentgenologically, but according to Weber,[25] "the contours of the tuberculous intestine have the rougher, more corrugated appearance, corresponding to a more irregular development of the ulcero-hyperplastic process." Retrograde filling of the ileum by barium enema brings out the regularly constricted lumen of the terminal portion of the ileum, as contrasted to the more irregularly constricted lumen of tuberculosis.

Nonspecific Ulcerative Colitis.—This should present no difficulties. There are always blood and pus in the stools in considerable amounts. Proctoscopy is helpful. This disease is the antithesis of tuberculous colitis, in that it usually begins in the rectum and proceeds cephalad, while the reverse is usually true of tuberculous disease of the colon. The bowel becomes evenly tubular and loses its haustrations, as compared to the more ragged changes in tuberculosis.

Funtional Disorders.—Functional disorders of the colon induced by psychic factors, continued use of laxatives or rough diet or disorders of bowel function produced by food allergy are common and must be differentiated. A careful clinical analysis may seem convincing, but the final word lies in the *x*-ray examination, since these disorders rarely produce changes which can be confused with tuberculous disease.

PROGNOSIS

The prognosis of intestinal tuberculosis today is most favorable. Nearly all patients with this disease should recover, provided the disease in the lung can be controlled and the rather simple method of therapy to be outlined in the following section is thoroughly carried out. Such a hopeful picture did not exist until about twelve years ago, and only twenty-five years ago the prognosis was considered almost hopeless. Here is a concrete example of the great strides medicine is making in conquering disease.

TREATMENT

Prophylactic Treatment.—The incompleteness and the futility of the treatment of intestinal tuberculosis without assiduous emphasis on prophylaxis are not widely enough recognized. Preventive medicine and surgery may be practiced in this field with most gratifying results. The success with which active treatment of the disease is attended is negligible in comparison with the reduced incidence of intestinal involvement to be produced by considering prophylaxis in its most direct sense. This leads immediately to consideration, first, of the infecting mechanism and, second, of the tissue infected.

The tubercle bacilli producing the lesions in the bowel originate in the lung lesion and arrive at the site of predilection through the alimentary tract. Habitual swallowing of sputum, which is common, should be stopped. Open areas of ulcerating disease in the lung are the source, then, of the infecting organism, and insistent emphasis should be placed on the necessity of stopping the steady stream of sputum, with its virulent bacilli, to the intestinal mucosa. Such procedure has always seemed logical and is recently becoming realized rather than theorized on. Bed rest for the early lung lesion and phrenic paralysis, intrapleural and extrapleural pneumothorax, thoracoplasty and other methods of surgical collapse for the more advanced lesions are urgently indicated, primarily to heal lung lesions and secondarily to stop transmission of the disease to the intestine and other organs.

The area in the bowel most richly supplied with lymphatic tissue becomes infected with passing bacilli, as does all lymphatic tissue in the presence of adjacent tuberculosis. Contributing to the involvement in this area is the slowing up of bowel content and the freeing of tubercle bacilli by the process of digestion. The organisms fix themselves in the cecum and ileum. It is logical to assume that any factor acting in this region to reduce the resistance of the mucous membrane enhances the opportunity of the tubercle bacillus to gain a foothold. The maintenance of good digestive function and supplying the need of varied nourishment containing the indispensable food elements, minerals and vitamins, are most important in keeping the tissue at its optimum level of resistance. As a matter of routine, we give our patients with pulmonary tuberculosis 1 large tablespoonful of a good cod liver oil floated on 3 ounces of either orange or tomato juice three times a day, because it is our belief that this procedure lessens the incidence of bowel involvement. Bonafe[3] stated: "the dyspeptic tubercular is a candidate already designated for intestinal tuberculosis." All digestive symptoms should be carefully noted and alleviated in the manner most consistent with the aim of keeping the intestinal mucosa best nourished and least exposed to chemical, mechanical, infectious or parasitic trauma.

Active Treatment.—To those who see a great deal of pulmonary tuberculosis it is evident that just as associated bone and joint tuberculosis has much decreased in incidence over the past twenty years, so has intestinal tuberculosis. The great frequency of fulminating intestinal tuberculosis previously seen has perceptibly lessened. In the past, for the case of far-advanced pulmonary disease commonly encountered, with intestinal tuberculosis with severe diarrhea, little hope was held out for recovery. This prognosis was, and to a large extent probably still is, a legitimate one. Nevertheless, at the present time, when the diagnosis of intestinal involvement can be made early enough that a cure of the phthisis can be effected, more interest is being directed to and hope placed in methods of treatment, and with justification.

There is now considerable proof, in the form of comparative *x*-ray studies, postmortem findings and well founded opinion, that intestinal tuberculosis can and does heal. The healing, of course, is in large part provisional on the healing of the lung lesion and the stopping of entry of tubercle bacilli into the intestinal tract. Aside from the urgent necessity of this, which should be considered important in cure as well as in prophylaxis, much can be done in an active way to promote healing of tuberculosis of the intestine, a disease which has, on its own, a proved tendency to heal.

The patient should be placed at bed rest. The diet should be a soft, low residue one, containing adequate caloric value as determined for the individual case. Raw foods except strained fruit juices are best omitted. Foods such as nuts, excessive sweets, cabbage, corn, dried shelled peas and beans, pineapple, seedy berries, bran and ice cream, which stimulate peristalsis, should be omitted. Iced or cold or carbonated foods and drinks are best not used. Because the diet is restricted, it is important to provide essential vitamins. These food elements, which are essential in the physiochemical process of human metabolism, according to recent investigations, are intimately connected with the healing of tuberculous ulcers in the bowel. Thiamin is generally recognized as closely related to gastrointestinal function. McCarrison[18] found that in birds fed on a diet deficient in thiamin atrophic changes developed in the upper part of the intestine. Smith and McConkey[21] fed tuberculous sputum to guinea pigs whose diet was deficient in vitamin C, and in 32 of 37 animals intestinal ulceration developed. In the control group, intestinal lesions developed in 11 of 35. Grant[14] found scorbutic diets with excessive vitamin D failed to regenerate the epithelium and underlying mucosa after injury. However, with an abundance of both vitamin C and D in the diet, large necrotic ulcers healed quickly and completely.

Vitamins A, C and D are best supplied by the giving of cod liver oil and tomato or orange juice. The B complex is satisfactorily supplied in brewer's yeast. Ferrous sulfate should be given in a minimum of 12 grains daily, and when this does not suffice to bring the hemoglobin concentration and red cell count to normal or when there is intolerance to iron by mouth, it should be given parenterally—best in the form of iron cacodylate, 5 cubic centimeters of the common form intravenously twice weekly. Other helpful medicinal therapy is the use of calcium chloride or calcium gluconate intravenously in daily to semiweekly doses, depending on the severity of the indications. The gluconate probably has all the advantages of the chloride and none of its disadvantages. This medicament has at times a most gratifying effect on the uncontrollable diarrhea and on the nausea and pain, apparently by a specific sedative effect through the nervous system of the bowel consequent to lessening of its irritability. A powder containing equal parts of calcium phosphate, calcium carbonate and bismuth subcarbonate, in doses of from 1 to 6 drachms daily, is helpful in soothing the bowel and stopping the frequent stools. The newer colloidal aluminum preparations have been found satisfactory in easing the distress after meals. Powdered opium or the deodorized tincture of opium should not be withheld when necessary for the control of pain or diarrhea. The dose of the tincture may vary from 5 to 20 drops, given from two to six times in twenty-four hours. When given one-half hour before meals it makes for better food intake. In many cases anacidity is present, and hydrochloric acid should be given in full dosage.

The employment of artificial heliotherapy in the treatment rests on a sound clinical basis and is indispensable in the effectual management of intestinal tuberculosis. In the recent past sunlight has been used widely, but we think its use should be discontinued entirely, because of the impossibility of measuring doses and of possible bad results on the concomitant lung disease and because the lamp supplies more of the beneficial rays.

Our[24] patients are exposed to the rays of a mercury vapor ultraviolet lamp over the whole body, with the chest and eyes covered. Some authorities do not cover the chest, but we feel safer in doing so. The lamp is focused over the abdomen, and treatment is commonly begun with an exposure of one-half minute to the front and one-half minute to the back daily, with the burner placed at a distance of 36 inches. Each day thereafter the time of exposure is increased by one-half to one minute, according to the tolerance. Dark-skinned persons tolerate greater doses,, as a rule, than blondes. Burning is carefully avoided. The time is increased in this manner until the patient is getting thirty minutes' exposure on the back and thirty minutes on the front of the body. At this stage the distance of the lamp is gradually lowered to 30 inches. It is seldom necessary or desirable to increase the total time of irradiation to more than one hour or to have the burner closer than 30 inches. The schedule should not be too rigid, but should be adapted to the type of the patient's skin and the strength of the lamp.

Short periods of treatment are of little value; treatment should be continued until cure is effected. In most cases this varies from one to three years. Other methods of treatment, such as injection of oxygen into the peritoneal cavity and *x*-ray irradiation, have been recommended by some workers, but in our experience have not proved to be of added value.

Chemotherapy.—For about three years, considerable experimental work has been done on the treatment of tuberculosis with a group of drugs which are related to but are not sulfonamides and which are being called "sulfones."

This experimental work has been done on human beings as well as animals, and the results have been so encouraging, particularly on animals, that the day may not be far distant when, at last, an efficacious and safe chemotherapeutic agent for tuberculosis will be available.

Most of the work has been done with "promin" (sodium p, p^1-diaminodiphenylsulfone-N, N^1-didextrose sulfonate), which has proved notably effective and produced little toxic reaction in animals. Because it has, however, produced toxic reactions in human beings, other, closely related drugs are now being tried in the hope that one may be found which is effectual against the tubercle bacillus and at the same time not toxic.

HYPERTROPHIC TUBERCULOSIS OF THE INTESTINE

The existence of the hypertrophic type of tuberculosis of the bowel has been questioned, particularly in view of the recent interest in regional enteritis. There is as yet not sufficient evidence to remove it from its previously accepted status. The disease is characterized by a hyperplastic growth in the bowel, produced by attenuated tubercle bacilli and by tumor formation and a tendency to intestinal obstruction. It has been called scirrhous, nodular, sclerotic, neoplastic cecal tuberculosis and tuberculoma. There is some question as to its always being primary, but a careful assessment indicates that in at least 70 per cent of cases it is.

Hartman and Pilliet[15] first gave a detailed description and established the true nature of the tumor. It is characterized pathologically by marked round cell infiltration and much fibrous tissue, extensive thickening of the wall and narrowing of the lumen. It has a tendency to remain localized. It is a hard, thickened, immobile mass, usually tender to palpation. Linthicum[16] reported the absence of the disease in 7,698 cases of pulmonary tuberculosis, although secondary ulcerative enterocolitis was present in a majority. The rarity of the process is indicated in Davis'[9] report of 29 patients admitted in a period during which 1,123 patients with carcinoma of the colon were admitted. In the 29 cases distribution of the lesions was as follows:

Ileocecum	22	Ascending colon	1
Sigmoid flexure	3	Appendix	1
Hepatic flexure	1	Jejunum	1

In Lockhart-Mummery's[17] 100 cases, the lesion in 87 was in the cecal region.

This disorder is usually not associated with tuberculous disease elsewhere, though of Davis' patients 2 had tuberculosis in other organs. It is more common in England and has been more common in the United States in the past. The reduced incidence here is probably due to the lessened incidence of tuberculous milk. The differential diagnosis from carcinoma cannot be positively made without exploratory surgical measures.

The treatment is distinctly surgical, and excision or, for neglected disease, short circuiting by ileocolostomy is satisfactory. Heliotherapy or irradiation from the quartz lamp is beneficial and should be used when excision is not done.

TUBERCULOUS FISTULA IN ANO

Tuberculous anorectal fistula is a fistulous tract having an internal opening in the lower part of the bowel, usually at the mucocutaneous line, and an external opening in the skin near the anal opening and having as a causative organism the tubercle bacillus. It is similar to the purely pyogenic fistula, and absolute differentiation is in most cases difficult, even pathologically. The fistula follows injury to the mucous membrane, most commonly at the site of the crypts, which gives entrance to the infecting organism. Trauma may result from the presence of hard material in the stool, from severe diarrhea or from the use of enema tips. Abscess formation practically always accompanies the development. Fistulas may be complete, incomplete, multiple or complex.

The number of tuberculous fistulas seen in general practice has steadily been lowered in the past few years to a figure now apparently fixed at about 10 per cent of all fistulas seen. In tuberculous patients, particularly those with intestinal or pulmonary ulceration, 70 to 90 per cent of fistulas are tuberculous, and in nontuberculous patients they are seldom tuberculous. The conclusion that tuberculosis is a cause of anal fistula is supported by the observation that in persons with this disease in the lung or bowel there is a greatly increased incidence of fistula formation. Chisholm[7] found that 77 per cent of fistulas in tuberculous patients were caused by the tubercle bacillus. In over 40,000 collected general hospital admissions anal fistula was present in 0.27 per cent, while in over 6,000 collected cases of pulmonary tuberculosis anal fistula existed in 2.35 per cent. Tuberculous anal fistula is practically always secondary to tuberculosis elsewhere. Buie[6] said: "Although there is some possibility that primary tuberculosis may involve the structures of the anorectal region probably it occurs so rarely as to be a pathologic curiosity." Because of this, the presence of anal fistula should always prompt the examiner to examine the chest for a primary focus.

The treatment of the condition is surgical, along with control of the primary focus.

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CHAPTER XXV

THE PROBLEM OF THE VERMIFORM APPENDIX*

Appendicitis is one of the most important of surgical diseases and constitutes a public health problem.

The supreme misfortune which can befall a man is that theory outstrip performance—so said Leonardo da Vinci, one of the most accomplished men of all time. This ill fortune appears to have overtaken the surgeon in dealing with appendicitis, for whereas the technic of removal of the appendix in experienced hands has attained a standard of completion difficult to improve on, yet appendicitis continues to exact an unwarranted and unaccountably high mortality.

Here in the United States, where Fitz (1886) established the entity on a pathologic basis and gave the disease its name and where early excision of the acutely inflamed appendix was first advocated and practiced by McBurney (1889), the mortality of the disease is among the highest (Table 11). The pathologic studies of Fitz appeared to have found support in the experiments of von Zwalenburg (1904) and in the clinical observations of Wilkie (1931), yet the status of medical knowledge concerning the genesis of appendicitis in man cannot be described as other than chaotic.

Table 11.—Deaths From Appendicitis Per 10,000 of Population From Various Countries of the World†

Year	Country	Deaths per 10,000 population	Year	Country	Deaths per 10,000 population
1934	Canada	1.5	1935	Italy	0.7
1934	United States	1.4	1935	New Zealand	0.7
1935	Switzerland	1.3	1934	Norway	0.7
1933	Sweden	1.0	1935	Netherlands	0.5
1934	Union South Africa (white persons only)	1.0	1933	France	0.4
			1935	Hungary	0.4
1935	Australia	0.9	1934	Japan	0.4
1935	Denmark	0.9	1934	Greece	0.3
1935	Belgium	0.8	1933	Spain	0.3

Considerable recent improvement appears to be occurring in the mortality caused by appendicitis in the United States. In 1935, there were 16,142 deaths from appendicitis or 12.6 deaths per 100,000 population. The mortality for 1936 was approximately the same. In 1939, there were 14,113 deaths from appendicitis in this country; in 1940, 12,999 and in 1941, 10,789. The rates per 100,000 of population for these years were therefore 10.8, 9.9 and 8.2, respectively. There is room still for considerable additional improvement. It is to be hoped that, as the mechanical nature of the origin of appendicitis finds wider acceptance, a progressive decline in the mortality of the disease will occur.

THEORIES OF ORIGIN OF APPENDICITIS

On the one hand are physicians who insist that appendicitis is essentially of bacterial origin. Those who held to its hematogenous origin have been succeeded by those who contend that swallowed microörganisms from the nasopharynx lodged in the appendix and gave rise to inflammation. The late Professor Aschoff (1930) went so far as to assert that appendicitis is a specific bacterial disease (not unlike gonorrhea in its specificity) due to the enterococcus type B of Gundel, which he found as a usual inhabitant of the distal third of the normal appendix, while in the proximal two-thirds of the appendix was a mixed bacterial flora not unlike that of the cecum. What provocation causes these organisms lurking in the terminal recess of the appendix to become invasive Aschoff failed to state. On the other hand, some physicians insist that the occurrence of appendicitis is determined largely by such general factors as latitude, longitude, diet and habits of life.

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* The McArthur Lecture (Procedings of the Institute of Medicine of Chicago **12**, 266, 1939) constitutes the basis of this discussion.

† Taken from *Statistisches Jahrbuch fur das Deutsche Reich*, 1937, p. 30, under section of *internationale ubersichten.*

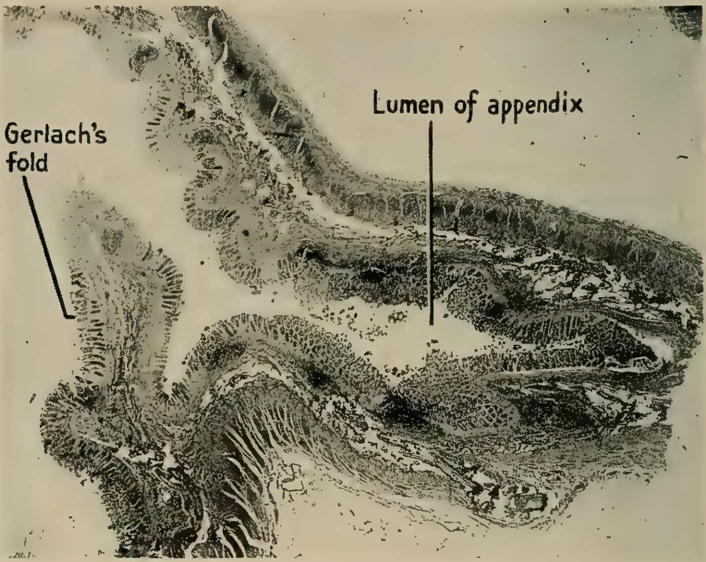

FIG. 106.—The more usual mucosal fold of Gerlach. Note the presence of only submucosa in it and the absence of muscle. (Wangensteen *et al.*, courtesy of *Annals of Surgery*.)

This confused state of opinion contributes unquestionably in no small measure to the mortality of the disease. Whereas a disease may be treated in an empiric fashion fairly successfully, an adequate appraisal of its nature lends invariably a tremendous impetus to the correction of defects in management. If the cause or causes of appendicitis were known, a more ready general acceptance by both the medical profession and the public would be found for advised therapeutic procedures. Physicians cannot confront the public with an intelligent program directed at solution of the appendicitis problem and gain its confidence while their own ideas of the origin of the disease are in so chaotic a state.

Mindful of the paucity of specific infections in the intestinal canal and the bad relation structurally of this narrow diverticulum to the remainder of the intestinal canal, a number of my surgical colleagues and I have devoted much time to a study of the obstructive origins of appendicitis. These studies, which largely have been published already, serve to emphasize the significance of the mechanical factors in appendicitis.

1. **The Anatomy of the Appendix.**—**Gerlach's Valve.**—Gerlach (1847) related the instance of a boy aged fifteen years with abdominal pain to whom he administered castor oil in repeated doses and later gave enemas. Necropsy showed perforation at the base of the vermiform appendix and a fecal concretion in the lumen of the appendix beyond the site of perforation. On opening the cecum the author found a mucosal fold overlying the appendiceal orifice. Among 9 necropsies such a mucosal fold was observed four times. Much debate has hedged about the significance of this fold. In the main, both anatomists and clinicians, however, have discredited it largely as having any importance.

Observations made by Dr. R. E. Buirge in my clinic are summarized in Table 12. One or more mucosal folds overlie the appendiceal orifice, usually in the superior cecal wall, in 81.5 per cent of cases. The primary fold overlying the appendiceal orifice is referred to in Table 12 as Gerlach's fold.

TABLE 12.—MUCOSAL FOLDS ABOUT THE APPENDICEAL ORIFICE*

Folds present on superior and inferior cecal wall	No. of specimens		Percentage	
Gerlach's mucosal fold	183		34.8	
Gerlach's and one semilunar mucosal fold	147		27.9	
Gerlach's and two semilunar mucosal folds	82		15.6	
Gerlach's and three semilunar mucosal folds	1		.2	
Gerlach's and Nanninga's mucosal fold	16		3.0	
Total with Gerlach's mucosal folds		429		81.5
No folds about the orifice	89		16.9	
No Gerlach fold; one secondary mucosal fold	1		.2	
Longitudinal mucosal folds	5		1.0	
Complete ring	2		.4	
Total without Gerlach folds		97		18.5
Total orifices		526		100.0

The extent to which obscuration of the appendiceal orifice occurred through the agency of mucosal folds is indicated in Table 13. In all fetal specimens there was direct continuity between the appendiceal lumen and the cecal cavity. The majority of appendiceal orifices (80 per cent) were less than 6 mm. in diameter. A large number of specimens in which these folds were prominent were subjected to microscopic examination, and in only 3 (all fetal specimens) was circular muscle projected definitely into the fold. It is apparent, therefore, that Gerlach's fold in the adult has none of the characters of a musculosphincteric valve.

TABLE 13.—INCIDENCE OF OBSCURATION OF APPENDICEAL ORIFICES BY MUCOSAL FOLDS

	Hidden	Partially hidden	Not hidden	Total
Fetal	0	0	57 (100.0%)	57
Others	57 (12.3%)	77 (16.5%)	331 (71.2%)	465
Total	57 (10.9%)	77 (14.8%)	388 (74.3%)	522

My interpretation is that the purpose of Gerlach's valve is to interfere with or preclude filling of the lumen of the appendix. It is difficult to believe that it can interfere with emptying.

Musculature of the Appendicocecal Junction.—Histologic study of blocks 1 centimeter in length cut from the appendicocecal junction failed to disclose any evidence of a sphincter muscle. A distinct thickening, however, of the circular muscle on the medial or ileal side of the union was observed in 59 per cent of 250 specimens, which may suggest a "signet ring" type of circular sphincter.

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* Mucosal folds about the appendiceal orifice of 526 adults and fetuses, or 77.92 per cent of the total series of 675 specimens.

A variable diminution of muscle fibers continues over to the appendix from the cecum. The dispersion of the longitudinal fibers of *Taenia coli* over the appendix was studied with a microdissector in 18 cases. Longitudinal muscle bands divide themselves into three layers, superficial, middle and deep. The deep fibers attach themselves rather intimately to the circular fibers at the apex of the cecum. The decussation of the longitudinal cecal bands about the appendix occurred in somewhat more than half the cases in an iris diaphragm-like manner about the base of the appendix.

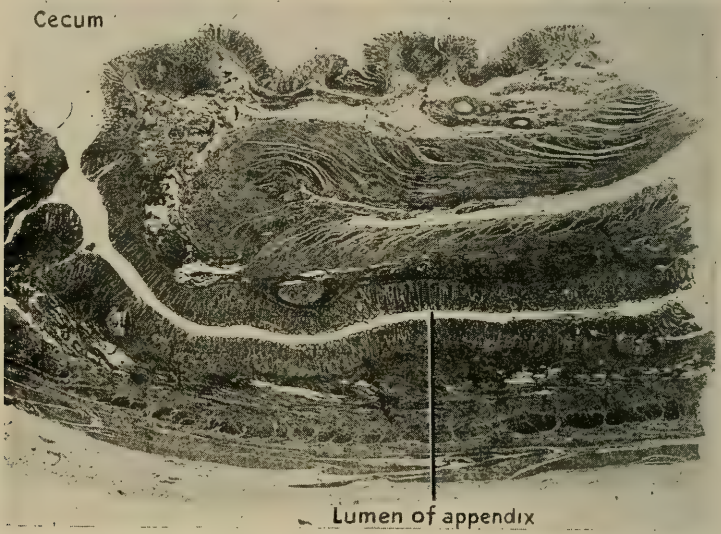

Fig. 107.—On the upper or medial wall of the appendicocecal union, the thickening of the muscle at the apex is apparent—a frequent occurrence. (Wangensteen *et al.*, courtesy of *Annals of Surgery*.)

Type of Appendicocecal Union.—Treves (1885) studied the external form of the appendicocecal union and established four general types. A summary of the types of appendicocecal union observed in 262 specimens, 63 of which were from fetuses, is shown in Table 14. All the fetal appendixes and the majority of those from patients below one year fell into type 1, in which the appendix constitutes the true center of the cecal apex and a funnel-shaped continuation of it. The type 2 cecum is similar to the type 1, except that it is sacculated evenly on both sides and there is not, as in type 1, a gradual fusion of the lumens of appendix and cecum but, on the contrary, a sudden transition. In type 3 the site of appendicocecal union is forced far medial to the left toward the ileocecal valve because of the greater sacculation on the lateral aspect of the cecum. In type 4 this sacculation has become so great that the medial wall of the cecum is practically absent, in consequence of which the base of the appendix comes to lie near the termination of the ileum.

TABLE 14.—CLASSIFICATION OF CECUMS

	No.	Treves' Type 1	Treves' Type 2	Treves' Type 3	Treves Type 4
Fetal	63	63	——	——	——
Term—1 year	25	20	——	5	——
1–10 years	12	5	——	6	1
11–20 years	7	1	——	5	1
21–30 years	9	1	——	8	——
31–40 years	16	1	1	13	1
41–50 years	33	3	1	26	
51–60 years	37	7	1	27	2
61–70 years	33	2	2	25	4
71–80 years	23	2	——	18	3
81–84 years	4	——	——	4	——
Total	262	105 (40.1)	5 (1.0)	137 (52.3)	15 (5.7)
Fetal	63	63 (100.0)	——	——	——
Term—84 years	199	42 (21.1)	5 (2.5)	137 (68.9)	15 (7.5)
Term—10 years	37	25 (67.6)	——	11 (29.7)	1 (2.7)
11–84 years	162	17 (10.5)	5 (3.1)	126 (77.8)	14 (8.6)
Treves	100	(2.0)	(3.0)	(90.0)	(5.0)
Berry	100	(10.0)	(6.0)	(80.0)	(4.0)

Lymphoid Tissue and Glands of the Mucosa.—The lymphoid tissue has been the subject of many published inquiries, and considerable information is available relating to the lymphoid structure of the appendix. The vermiform appendix of man has been referred to frequently as the tonsil of the abdomen. It has been said to contain as much lymphoid tissue as the entire colon exclusive of the cecum. The lymphoid follicles have been estimated by Liebeck (1924) to occupy 30 per cent of the mucosal surface of the appendix, the variation lying between 8.2 and 52.8 per cent. According to Berry and Lack (1905–1906), the lymphoid follicles do not make their appearance until shortly after birth. In the section of fetal appendixes in which the musculature of the appendicocecal union was studied, lymphoid follicles were encountered now and then, however. Nagoya (1913) noted fairly complete development of the lymphoid tissue in the appendix at the end of the second month of life, attaining its maximum growth between the eleventh and the sixteenth year, a little later than the lymphoid tissue of the rest of the body. In the main, sections of the distal portion of the appendix, Nagoya found, exhibit more lymphoid tissue than do sections from the middle or proximal portion. Yet I have the impression that persons of advanced years have the lymphoid tissue in lesser amounts toward the tip. Nagoya has counted as many as 42 lymph follicles in a circular section of the appendix from an eleven year old child. In the appendix of a man of seventy-two years, as few as 2 or 3 follicles were noted in a section, corresponding closely with the number present in infants of four to six weeks. Nagoya estimated that at the extremes of life the lymphoid tissue in the appendix approximates in amount only a twentieth of that present when its development is maximal, in the late adolescent years.

The lymphoid tissue of the appendix not only is submucosal but often extends well into the mucosa, being covered by a very thin layer of epithelium and occasionally by none at all. The absence or virtual absence of mucosa overlying the lymphoid follicles accounts in all likelihood for the occasional presence of epithelial cells, lymphocytes and leukocytes in the appendiceal lumen without evidence of ulceration of the mucosal layer.

The status of the glands of Leiberkühn lining the appendiceal mucosa parallels closely that of the lymphoid follicles. The greatest number of glands Nagoya observed was in specimens from persons between the eleventh and sixteenth year, when the growth of lymphoid tissue was greatest. In contrast with the distribution of lymphoid tissue, the glands of Lieberkühn, Nagoya observed, are more numerous in the middle than in the distal segment of the appendix. In the appendix of a sixteen year old child Nagoya counted 140 glands in a circular section from the mid-portion and 95 in a section from the distal segment. The glandular development of the mucosa is fairly complete in infants at five to six months. A section of the appendix of a seven month fetus exhibited only 7 glands; that of a seventy-two year old man, 20 glands.

The Luminal Capacity of the Appendix is surprisingly small. In a number of appendixes which were not obstructed, the measured luminal capacity at 20 centimeters of water pressure did not exceed 0.23 cubic centimeters; at 60 centimeters pressure the highest luminal capacity was 0.7 cubic centimeter. At 100 centimeters of water pressure, the volume was correspondingly greater. The volume of appendixes recovered post mortem, when the resistance to luminal perfusion is absent, was, of course, greater.

Of three normal appendixes excised coincidentally during the course of abdominal operations, none could be ruptured by pressures as high as 2,400 centimeters of water (approximately 2.3 atmospheres) directly after excision. In this process a stretch of luminal capacity to about 5 cubic centimeters occurs. Gangrenous unruptured appendixes were found to break at very low pressures—one at 20 centimeters of water and another at 70 centimeters. The presence of an inflammatory reaction in the appendiceal wall decreases its strength tremendously.

The cecal appendage of the rabbit has a larger luminal capacity than the vermiform appendix of man,and its wall is considerably thinner. Its breaking strength was found to be only 120 to 150 centimeters of water.

2. **Physiologic Behavior of the Appendix.—Resistance to Luminal Outflow.**—When a needle is inserted through the distal end into the lumen of the vermiform appendix, a resistance to inflow of fluid is encountered. The order of magnitude of this resistance is indicated in Table 15. Vermiform appendixes removed from cadavers exhibit practically no resistance to luminal perfusion, which is highest in appendixes acutely involved, less in the interval group and lowest in normal appendixes.

TABLE 15.—RESISTANCE TO INTRALUMINAL OUTFLOW*

	No. of cases	Centimeters of water pressure sustained			
		Average	Median	Maximum	Minimum
1. Normal	11	38.0	28	110	16
2. Interval	45	54.4	45	130	16
3. Acute	27	73.0	68	120	12†
4. Normal from cadavers	13	2.9	3	7	0

Excised specimens directly after removal exhibit the same or even greater grades of resistance to outflow than do appendixes *in situ* with the mesentery intact. If, however, the appendix is left in a container at room temperature, in thirty or forty minutes the resistance to luminal outflow

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* This table also contains pressure determinations made on the excised appendix directly after removal.

† This appendix was infested with pinworms; the next lowest reading in this group (30 cm.) occurred in 4 cases.

becomes minimal. The resistance is preserved, however, if the appendix is kept in the icebox at a temperature between 2 and 7 C. The pressure in appendixes so treated, however, is about one-third of that obtained immediately postoperatively. When the appendix is excised it shrinks in length. There appears to be a fairly direct correlation between the grade of shortening and the increase in resistance to luminal outflow after excision. This resistance to luminal outflow persists after amputation of successive segments, indicating that resistance to luminal outflow is a property of each and every segment of the appendix and represents, in fact, the resistance of the circular muscle of the appendix to distention. The resistance to inflow is of the same order of magnitude as resistance to outflow.

Appendicostomy Studies.—(*a*) *Resistance to Luminal Outflow and Suggestion of Fluid Secretion.*—Appendicostomy was done in a small group of cases in which colostomy was performed for carcinoma of the colon or rectum. Table 16 indicates that the resistance to luminal outflow is essentially of the order of magnitude found for the interval and normal groups in Table 15. From 1 to 2 cubic centimeters of fluid can be collected daily from an unobstructed appendicostomy opening through a small catheter (no. 8 French urethral) tied into the lumen of the appendix, and pressures as high as 60 centimeters of water can develop in an unobstructed appendicostomy opening. The latter finding in particular suggested that the vermiform appendix of man probably secretes fluid. In the collection of fluid through an inlying tube, however, it could not be gainsaid that the fluid came from the cecum. Proof of the origin of this fluid from the appendiceal lumen will be cited presently.

TABLE 16.—RESISTANCE OF THE APPENDIX TO INTRALUMINAL OUTFLOW AFTER APPENDICOSTOMY

No. of cases	Centimeters of water pressure sustained			
	Average	Median	Maximum	Minimum
12	47.7	42.0	100.0	8.75

(*b*) *Injection of Bacteria.*—Placement of bacteria recovered from persons with acute suppurative appendicitis in the lumen after appendicostomy appeared to be tolerated without symptoms. In the light of Aschoff's contention relating to the specificity of the infection in appendicitis, one might have expected some febrile response or evidence of reaction.

(*c*) *Retention of Foreign Bodies.*—A single bird shot (no. 9) was placed in the lumen after appendicostomy in several cases. One was extruded into the colon with evidence of pain within two hours, as indicated by a roentgen film. In another the shot was retained for two months. Twenty-four to thirty-six hours was the usual length of retention. Occasionally the shot was expelled through the external stoma onto the dressings.

(*d*) *Spectrographic Evidence of Barium Retention.*—After the administration of barium enemas excised appendixes showed the barium lines in the spectrum at 4,554 and 2,332 Angström units. In 13 cases an appendix removed from six to seven hundred and ninety days after the administration of a barium enema, with which it had not been visualized by roentgen examination, failed to show spectrophotometric evidence of barium. In 4 other instances, in which the appendix was visualized by roentgen examination and removed ten, thirteen, ninety-three and two hundred and fifty-seven days after the barium enema, no spectrographic evidence of barium retention was found. In 6 others, however, in which the appendix had been visualized on roentgen examination from eight hours to six days prior to appendectomy, barium was detected by the spectrophotometric method, the approximate concentration in the luminal contents varying from 0.05 to 10 per cent. In patients who were known not to have had barium for roentgen examination at any time, the removed appendixes and their contents showed no trace of barium by this method of examination.

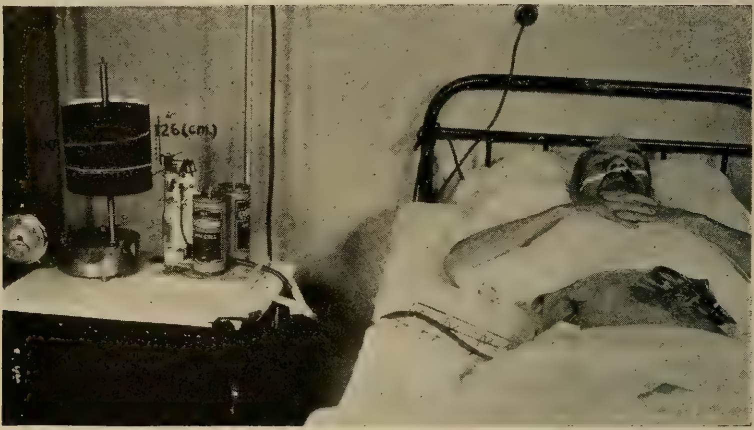

Fig. 108.—Tracing being made on Mr. T. W., aged sixty-eight years (Table 17, Case 1). The appendix has been exteriorized and ligated at its base. The slope of the rise of pressure is indicated on the smoked drum. The colostomy site is shown on the left, and the patient is apparently comfortable.

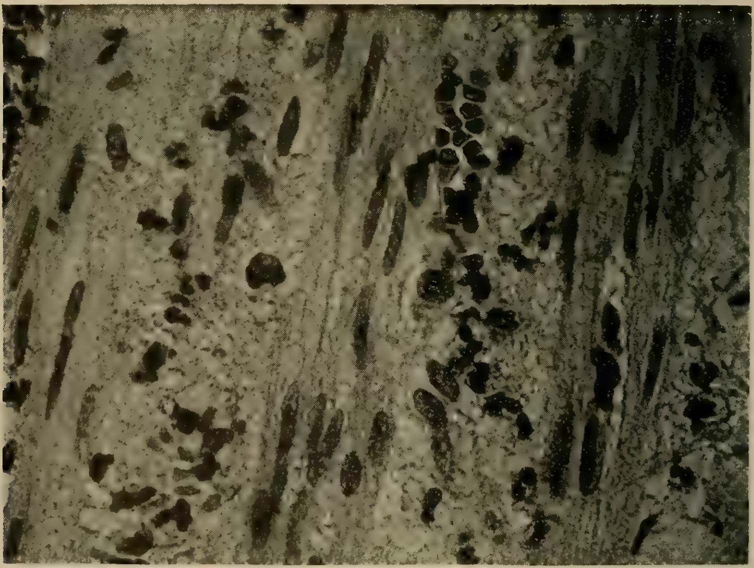

Fig. 109.—Section through muscle layer after pressure (× 500). Note the polymorphonuclear infiltration between the spindle-shaped muscle nuclei.

3. Proof of the Secretory Activity of the Vermiform Appendix.—

Method.—The pressure tracings made on unobstructed appendicostomy openings, in which gradual increases of intraluminal tension to as high as 60 centimeters of water were noted, suggested that the appendix secretes fluid. It was only with reluctance that a direct experiment was established in which the base of the exteriorized appendix was ligated, but over many months a suitable technic was worked out. In the first few instances a Bloch-Mikulicz type of operative exteriorization was done on the terminal part of the ileum and proximal part of the colon for carcinoma of the ascending colon. The blood supply of the entire exteriorized segment was left intact, and after the early operative convalescence had been safely passed, the base of the appendix was ligated. Intermittent pain with fever and leukocytosis was noted, and the increasing distention of the appendix could be kept under constant observation. Incannulation for graphic recording of pressure effects was done also. The process was not allowed to go on to spontaneous perforation of the appendix, the entire exteriorized segment being removed with the cautery when the necessary information had been obtained.

Table 17.—Studies of Secretory Capacity of Obstructed Exteriorized Appendix in Man

Patient	Sex	Age	Maximum pressure (cm. water)	Time required to reach maximum pressure (hours)	Time maximal pressure was sustained (hours)	Total fluid after end of recording (cc.)	Period of fluid collection (days)	Lapse of time between onset of experiment and removal of appendix	Histologic study	
									Control section	After pressure*
1. T. W.	M	68	126	22	2¾	3½	2	25 hours	Good mucosa	A.D.A.
2. O. N.	M	47	125	14¼	½	12½	6	3 days	Good mucosa	A.D.A. with necrosis
3. G. L.	F	33	114	35	14	3½	5	50 hours	Good mucosa	A.D.A.
4. P. G.	M	70	92	14½	7½	1½	2	48 hours	Good mucosa	A.D.A.
5. C. P.	M	56	90	16½	3	½	1	20 hours	Good mucosa	A.D.A.; loss of mucosa with fragmentation of muscle
6. U. T.	M	53	86	25½	0	. .	. .	Not removed	Good mucosa	No scetions
7. R. A.	M	29	85	27	0	7	7	Not removed†	Good mucosa	
8. M. K.	M	54	60	3¼	5½	½	2	Not removed†	Good mucosa	No sections
9. W. P.	M	45	42	12	9	0	0	21 hours	No sections	Mild A.D.A. with exudate in lumen
10. F. H.	F	60	32	7	0	5½	5	2 months	No sections	
11. P. S.	M	73	24	24	0	0	. . .	Not removed†	Atrophic mucosa distal end	
12. W. H.	M	53	20¶	. .	. . .	. .	. .	Not removed	Good mucosa	
13. T. C.	M	66	20	24	0	0	2	Not removed	Much fat in submucosa	
14. A. O.	F	53	17	20	0	7.2	8	Not removed	Fair mucosa with much lymphoid tissue	No sections
15. E. B.	M	58	15	18	0	0	. . .	Not removed†	Atrophic mucosa with much fat	No sections
16. W. B.	M	67	11	17	0	0	. . .	Not removed†	Atrophic mucosa with much fat	No sections
17. A. B.	F	41	8	2	24	7.4	13	13 days	No mucosa in control	Serositis; few leukocytes in muscle layer
18. J .S.	M	57	6	25	0	0	. . .	Not removed	No mucosa in control	No sections
19. A. T.	M	62	5	1	18	1.1	4	Not removed†	No mucosa in control	No sections
20. M. F.	M	75‡	0	. . .	. . .	0	. . .	26 hours	No mucosa in control	Mucus with leukocytes in lumen
21. A. C.	F	61‡	0	. . .	6 days	0	. . .	6 days	No sections	No sections
22. G. B.	M	53§	0	. . .	. . .	1	2	6 days	No sections	No sections

* A.D.A. indicates acute diffuse appendicitis.

† Too short for removal.

‡ Short mesentery, appendix under tension when exteriorized.

§ Appendix devascularized during exteriorization.

¶ See text: pressure not allowed to rise above 20 centimeters.

(*a*) *Secretory Behavior in Man.*—Experience appeared to suggest that the initial premise of secretory behavior on the part of the appendix was correct. Gradually a technic of sewing the base of the cecum to the anterior abdominal wall and ligating the base of the appendix was worked out when colostomy was done for carcinoma. The evidence relating to the secretory activity of the appendix of man is summarized in Table 17. No patients came to harm through the formation of appendicostomy openings which were obstructed. Obstructed appendixes were not allowed to go on to perforation, and when the secretory behavior of the appendix had been determined satisfactorily the closed recording system was broken and secreted fluid was collected by means of an inlying cannula in the tip of the appendix, in a small Wassermann glass tube at atmospheric pressure. On completion of all the necessary operative procedures for the primary surgical condition, extraperitoneal excision of the appendix was done if it continued to secrete. The skin grows over unobstructed appendicostomy openings quickly if the appendix is cut off flush with the skin.

(*b*) *Secretory Behavior of the Cecal Appendage in Various Animals.*—While a satisfactory and safe method of obstructing appendicostomy openings in man was being evolved, the behavior of the cecal appendage in a large number of animals was determined. Obstruction of the cecal appendage of the dog is unattended by inflammatory reaction if the lumen of the appendage is washed out; if, on the contrary, obstruction is established when feces distend the appendage, the development of an inflammatory reaction is the rule.

Obstruction of the cecal appendage was established similarly in a large group of animals, none of which gave evidence of secretory behavior in this segment of the gut. More than one animal was available for most of the investigations, and in most instances protracted graphic tracings were made of the pressure relation within the obstructed cecal appendage. The list of animals in which the cecal appendage gave no evidence of secreting fluid or developing sustained intraluminal pressure under conditions of obstruction follows (26 species of animals were studied):

Fowl: duck, goose, chicken, pigeon
Carnivorous mammals: dog, red fox, cat, tiger
Rodents: gray squirrel, striped gopher, rat, guinea pig, procupine
Domestic animals: hog, sheep, calf
Monkeys: marmoset, ring-tailed, macaque

The skunk, raccoon and bear were examined, but these animals were found to have no cecal appendage. Excised specimens of the ileocecal segment from the walrus and baboon (Doguera type), lent by Dr. George A. Barnett of Chicago, were found to be without a cecal appendage.

(*c*) *Obstruction of the Vermiform Cecal Appendage of the Rabbit.*—Ligature of the base was followed by rupture as early as three and one-half hours after the establishment of obstruction. The majority of animals (75 per cent) will exhibit perforation after ten hours. A gangrenous process was observed frequently in animals in which obstruction had been present for eight hours.

Incannulation is followed almost invariably by a fairly high secretory pressure, far more constantly than in man's appendix, in which occasionally no evidence of secretory pressure is observed. Pressures of 60 to 70 and occasionally of 90 centimeters of water are the rule, and the highest sustained pressure was 136 centimeters of water, 10 centimeters higher than the highest pressure in man.

The oral administration of cathartics or the intravenous use of hypertonic saline solution does not augment fluid secretion or lessen the interval over which perforation of the obstructed cecal appendage of the rabbit occurs. The hazard inherent in their use appears to lie in the breaking of a seal which the perforated vermiform appendage has established with adjacent tissues; cathartics in augmenting contractile activity of the gut preclude sealing of the perforation and enhance the danger of a wider spread of the spilled contents from the obstructed lumen.

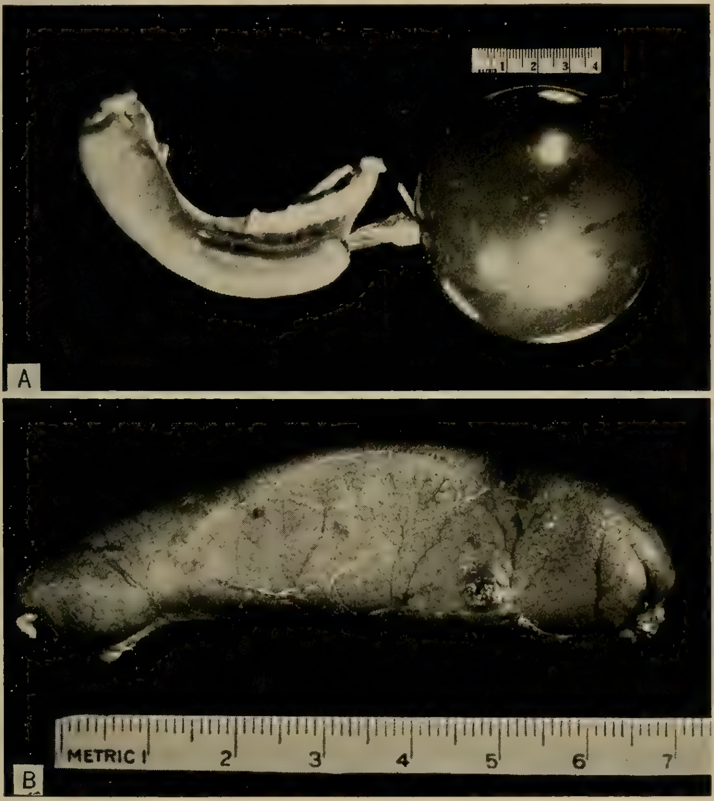

Fig. 110.—*A*, method of collecting fluid from the vermiform cecal appendage of the rabbit in a condom type of balloon in the peritoneal cavity. Note the lack of reaction in the appendage (histologically it was normal). *B*, another rabbit's appendage which perforated somewhat more than five hours after obstruction. Note the site of perforation near the mesentery. Microscopically a diffuse cellular infiltration of the wall was present. (Wangensteen *et al.*, courtesy of *Annals of Surgery*.)

(*d*) *Secretory Capacity of the Vermiform Appendix in Anthropoid Apes.*—Two gibbons and 3 chimpanzees were available for investigation. In the gibbon a maximal intraluminal pressure of 19 centimeters of water developed; this was sustained for only a short time. Histologic evidence of leukocytic invasion of the walls of the appendix was not observed. Serositis of the exteriorized segment was, of course, present. These sections constituted excellent controls, in that no leukocytic invasion of the appendiceal wall attended incannulation when a sustained secretory pressure failed to develop.

All 3 chimpanzees exhibited good evidence of an active secretory mechanism. The highest pressure reached was 106 centimeters of water thirty-three hours after the establishment of obstruction. This pressure was sustained for three hours before perforation occurred.

4. **Nature of the Fluid Secreted.**—The tremendous secretory capacity of the rabbit's vermiform appendage has afforded an excellent opportunity for the collection of fluid. The voluminal capacity of the rabbit's cecal appendage at the time of bursting is in the neighborhood of 16 to 20 cubic centimeters. Twenty cubic centimeters of fluid may be collected usually in about six hours in an attached balloon allowed to remain in the peritoneal cavity. The fluid is thin and serous, with free admixture of mucus. The *p*H of the fluid collected from the vermiform appendage of the rabbit when its base is ligated has varied from 8.78 to 7.12 and is usually distinctly on the alkaline side. The presence of such digestive ferments as sucrase, maltase and erepsin was demonstrated in the fluid as collected. After Berkefeld filtration to remove bacterial activity no enzymes could be found in the fluid.

The *p*H of fluid collected from the obstructed appendix of man was found to vary between 6 and 8.28, with a definite tendency to a lower *p*H than that of the rabbit. Mucin was found on all examinations, and the presence of amylase and erepsin was demonstrated.

As active secretory behavior in the vermiform appendix is wholly unexpected in the light of the usual concept of its function, it would be fitting if a morphologic explanation were forthcoming. It is not likely, however, that study of the appendiceal epithelium will supply the answer.

5. **Observed Histologic Reactions in Obstructed Appendixes Which Secrete Fluid.**—The time element relates itself intimately to the character of the cellular reaction provoked. In rabbits in which perforation followed within three or four hours after ligature of the base of the appendix, the resultant leukocytic reaction was minimal usually and concerned only the mucosa and the subserous coat. When, however, perforation occurred only after the lapse of ten to fourteen hours, a gangrenous process with pronounced cellular reaction involving all the walls was usually observed. When great increases of intraluminal pressure in the exteriorized appendix of man attended obstruction, erosion of the mucosa and an intense leukocytic invasion of all the walls, largely polymorphonuclear, occurred. In contrast to the diffuse cellular reaction throughout the entire wall noted in the 3 chimpanzees, all of which showed sustained intraluminal pressure, the gibbons, who showed no evidence of fluid secretion, had appendixes normal histologically save for serositis attending the exteriorization. In rabbits, when the intraluminal pressure was not allowed to exceed 6 centimeters of water by removal of successive increments of secreted fluid, histologic structural changes were not observed. When the intraluminal pressure was allowed to rise to and maintain itself at 20 centimeters of water, an acute diffuse process in the wall was observed in one case on histologic study; in another gangrene occurred, and in a third perforation was observed.

Gram-Weigert tissue stains of the rabbit's vermiform appendage show that bacteria are present normally in the submucosal lymphoid tissue.

That all lymphoid tissue may harbor bacteria under normal conditions is conceded generally. In man bacteria were observed occasionally below the surface epithelium of the appendix, but by no means as commonly as in the rabbit. Both Waetzold (1907) and Bowers (1938) have noted that bacteria may be demonstrated readily in the wall of the appendix if after excision it is not immersed in a fixative solution immediately. Bowers observed a high incidence of bacteria in the tissues of the appendiceal wall of man with acute appendicitis. When one contemplates the anoxic effects of high (secretory) intraluminal pressures on the tissues and the encouragement lent bacteria thereby, as well as the disseminating force of increased hydrostatic pressure, it is apparent that the infective factor is invoked early by obstruction of the appendiceal lumen.

Much remains to be learned concerning the cellular nature of defense reactions in general. To this an evaluation of the early histologic processes observed in spontaneous appendicitis in man is no exception.

NECESSITY FOR REVISION OF PATHOLOGISTS' CONCEPT OF APPENDICITIS

All pathologists with the exception of Aschoff and his followers have conceded freely that in some cases appendicitis has its origin, at least in part, on the basis of obstruction. In fact, many pathologists would agree that in a large number of cases acute appendicitis is solely obstructive in origin. What the origin may be when no definite pathologic evidence of obstruction is present is bu no means a matter of common agreement.

Pathologists recognize essentially the following types of disease:

1. Appendicitis in which the inflammatory reaction is limited to the mucosa (catarrhal, *primärinfekt*).
2. A diffuse inflammatory process involving all the walls (diffuse, phlegmonous, ulcerative, gangrenous, perforative).
3. A subserosal perivascular leukocytic invasion, which may occur independently or accompany mucosal lesions.
4. Healing phases of acute appendicitis, exhibiting granulation tissue reactions and lumen obliteration of varying grades, displacement of lymph follicles into muscular and subserous coats, invasion and replacement of structure of appendiceal wall with fat and mucocele formation.

The more severe grades of appendicitis, such as diffuse leukocytic invasion of all the walls with attendant phlegmonous, ulcerative, gangrenous or perforative changes, may all be reproduced experimentally by luminal distention. The lesser reactions, in which leukocytic invasion is limited to the mucosa and subserosa, are observed also with induced obstruction when the secretory pressure does not maintain itself at a high level. Seng (1930) has shown that there is a generous network of lymphatic vessels going out from the mucosa of the appendix directly to the subserous coat, a finding which is not uncommon apparently in the intestinal canal as a whole (Patzelt, 1936). Perivascular infiltration around the vessels in the subserosa after low increases of intraluminal tension in the appendix is understandable therefore.

The *primärinfekt* which Aschoff described shades off on the one hand into a process of extension of epithelial cells through the goblet cells of the crypts of Lieberkühn, with occasional actual loss of the surface epithelium, and on the other hand into leukocytic invasion of the appendiceal wall.

The first is certainly a normal reaction. And whereas the collection of leukocytes in the appendiceal lumen with the appendix otherwise grossly and histologically normal is now and then considered as evidence of early acute appendicitis, it is in all probability normal. I have observed it in the vermiform appendix of man, and it was noted in the distal end of the appendix excised as a control section in a chimpanzee before obstruction and incannulation.

The migration of leukocytes through intact epithelial cells of the entire digestive tract is well known. Jassinowsky (1925, 1927) found that in the rabbit the migration of cells in all parts of the digestive tract other than the mouth (where it is essentially polymorphonuclear) is lymphocytic. The migration of lymphocytes into the appendiceal lumen he found to be the greatest per square unit of surface in the entire intestinal canal. By irrigating the surface with saline solution he estimated that 14,500 lymphocytes per minute per square centimeter of surface were cast into the lumen. The desquamation of the surface epithelium was less intense in the appendix, where it was of the order of magnitude of 1,500 per minute per square centimeter of surface, as contrasted with the ileum, where it was 8,000, and with the upper part of the jejunum, where it was 7,300.

From studies of the histologic reaction attending obstruction of the vermiform appendages of man, chimpanzee and rabbit, it would appear that all the varieties of acute appendicitis recognized and observed by the pathologist may be produced experimentally by obstruction. The secretory pressure produces tissue injury and leukocytic invasion with pus formation, and all the varieties of appendicitis observed clinically may follow.

The pathologists' reluctance to accept the obstructive origin for certain types of appendicitis is occasioned in part probably by failure to find an obstructive mechanism even though a thin wall and a dilated lumen speak forcibly for such origin. What may have become of the obstructing agent? If a fecalith, the possibility of its having become dissolved by the ferments of the secreted fluid and broken up by the contractions of the appendiceal wall would appear to be good, at any rate.

Further, when with gangrenous appendicitis no obstructive agency is found and micrometric studies show the wall to be somewhat thick and the lumen small, it is not unlikely that these findings may be occasioned in part by the lapse of time after extrusion or solution of the obstructing fecalith. In the rabbit, anyway, if the obstruction is released in a gangrenous obstructed appendix (by cutting the occluding ligature, which has been tied down, on an encircling rubber tube), the findings just described are observed not infrequently.

THE ORIGIN OF APPENDICEAL OBSTRUCTIONS

The small lumen of the appendix, which exhibits normally a real resistance to outflow, indicates how substances which enter it may find difficulty in leaving. In addition, kinks and sharp bends in the axis of the structure as well as retrocecal fixation may constitute physical handicaps to ready evacuation. Extrinsic bands and intrinsic strictures, the latter the result of previous ulceration extending well into the submucosa, likewise may obstruct the appendix. Appendicoliths and the lymphoid tissue of the appendix itself constitute probably the most important agencies.

Any infection in which swelling of the lymphoid tissue of the appendix occurs may bring about closure of the lumen. The appendiceal occlusions which occur during measles, scarlet fever and other infectious fevers are likely to be brought about through such an agency.

Nature of Fecaliths.—Appendicoliths are formed *in situ* in all probability within the lumen of the appendix, because many are so large that only with the greatest difficulty could they have been forced into the appendix from the cecum. Most appendicoliths contain a central nucleus of undigested cellulose. Neumann (1925) claimed that swallowed hairs constitute a common nucleus of appendicoliths. Schuberg (1882) claimed at one time that the greater incidence of appendicitis in men than in women could be explained on the basis of "beard chewing." Beards and mustaches are no longer very common, yet appendicitis persists as a more frequent malady among men than women.

Appendicoliths may be hard and whitish or soft and brown. Mucus is undoubtedly an important constituent. The lamination of appendiceal concretions, which is fairly constant, is occasioned in all likelihood by the continued addition of mucus to the initial fecal body. The calcium which imparts hardness to the appendicolith arrives in the appendix from the main channel of the digestive tract, but is present also in the fluid secreted by the obstructed appendix.

In the series of cases of acute appendicitis studied recently by Bowers (1938) at this clinic, a fecalith was found to be present in 67 per cent; in 16 per cent of this number there were multiple appendicoliths.

The appendicolith is undoubtedly the most important single agency in the genesis of obstruction of the appendiceal lumen. Only Aschoff and his followers have denied it any significance. From the Friedrichshain Hospital in Berlin, Neumann (1925) reported having found appendicoliths in 544 of 1,847 excised appendixes (29.4 per cent). There were in this group 50 appendixes of children under six years of age. The incidence of appendicoliths in this group was 56 per cent, and in 42.9 per cent of this number hairs were present in the appendiceal concretions.

Swallowed foreign bodies, such as pins, small bones or lead shot, if lodged in the appendix may perforate its wall or give rise to appendiceal obstruction. Worms, especially *Oxyuris vermicularis*, are not uncommon in the appendix and doubtless provoke appendiceal colic occasionally.

Filling and Emptying of the Appendix.—When the manner in which the appendix fills is understood better, the development of appendiceal concretions will be more intelligible. The mucosal folds exist over the appendiceal orifice probably to preclude entry of intestinal contents into the appendiceal lumen. Fluid is secreted and may be collected from an unobstructed appendicostomy opening through its distal end on the anterior abdominal wall. Lead bird shot placed in the appendiceal lumen may be extruded on the anterior abdominal wall, but more often is expelled into the cecal lumen. Spectrophotometric studies of excised appendixes in which prior to operation administered barium was visualized within the lumen have shown that barium may be retained by fairly normal appendixes for as long as six days. In stenotic appendixes barium may be retained for months.

Sir Arthur Keith (1912) has described the cecocolonic sphincteric tract, a functional sphincter which he found on the ascending colon about 5 centimeters above the entry of the ileum into the cecum. Though not recognized by anatomists, a functional sphincter has been described at this site on the bowel by roentgenologists (Hirsch, 1924; Biedermann, 1932; and Morse, 1936). I have observed that the intraluminal pressure during digestion may be surprisingly high in this segment of the colon. Contractions on a small balloon passed down into the cecum and distended to a diameter of about 2 centimeters have been recorded with an amplitude of 20 to 30 mm. of mercury (27 to 40 cm. of water pressure). When pain is evoked, pressures in excess of 50 mm. of mercury have been noted. The competency of the ileocecal valve and sphincter against regurgitation into the ileum has been well established. It is not difficult to understand how the vermiform appendix would fill readily in the presence of a high hydrostatic filtration pressure in the cecum if a functional sphincter is present on the ascending colon. Dennis (1941) expressed doubt that a functional mechanism of obstruction (spasm) may be responsible for initiating changes similar to those attending an actual obstruction of the lumen of the appendix.

THE MYTH OF APPENDICITIS AND DIET

It is believed widely that appendicitis is a disease of civilization and culture, in which diet and lack of physical activity are the chief determinants. Among others, the following dietary factors have been alleged to play an important role in the causation of appendicits: increased consumption of meat and especially frozen and preserved meats, the eating of bananas, increased consumption of sugar and the eating of inadequate amounts of cellulose. The strange thing is that bits of cellulose constitute often the central nucleus of appendicoliths, which play an important role in the genesis of acute appendicitis.

The source of the myth that appendicitis is a dietary disease would appear to have had its origin in occasional reports emanating from China relating to the rarity of appendicitis, and similar reports have since come from other parts of the world where white persons are in the minority. However, the available papers of surgeons working in well established hospitals in China show that appendicitis is far more common in that country than one is taught to believe. Whereas the diet of the Chinese has apparently remained essentially the same for centuries, appendicitis is being more frequently discovered as the Chinese accept the medicine of the white physician.

The same can be said for other countries. Reports from Java, India and the Philippine Islands show that appendicitis is a not uncommon surgical disorder. Burdette (1918) said that he was unable to detect the slightest anatomic difference in the appendixes of Americans, English, Japanese, Chinese and Malays and that no one race was more disposed to appendicitis than another. That the mortality of appendicitis in Japan and South Africa is not negligible is to be noted in the summarical mortality table of appendicitis by countries (Table 11).

Moreover, the mortality of appendictis among Negroes in the United States is higher than among white persons. Table 18, from Dublin and Lotka's 1937 computation (Metropolitan Life Insurance Statistics), indicates that the death rate per 100,000 was higher during each period of study for both Negro males and females than for white persons of the same ages (from one to seventy-four years).

Excision of the appendix was rare in American and European hospitals before 1893, though an appendiceal abscess was incised now and then. This may in part explain why appendicitis does not appear to be so common a surgical disorder in countries where modern hospitals are relatively recent innovations.

Table 18.—Comparative Mortality Among White Persons and Negroes in the United States From Appendicitis, 1911 to 1935*

Metropolitan Life Insurance Company, Industrial Department, 1911 to 1935

	Death rates per 100,000					
	Males			Females		
Age period (years)	1911 to 1935	1931 to 1935	1911 to 1915	1911 to 1935	1931 to 1935	1911 to 1915
White —1 to 74 . . .	14.8	15.5	12.9	10.9	10.7	10.1
Colored —1 to 74 . . .	15.3	16.1	13.6	13.3	13.3	11.1

APPENDICITIS, A PUBLIC HEALTH PROBLEM

In 1935 there were 16,142 deaths from appendicitis in the United States (Mortality Statistics, United States Census). It ranked as the fifteenth most important cause of death among persons of all ages. Among the policyholders of the Metropolitan Life Insurance Company between the ages of one and seventy-four, a study extending from 1911 to 1935 showed that appendicitis was ninth in order among causes of death. Among gainfully employed men between the ages of fifteen and sixty-four, appendicitis ranked eighth. It accounts for more deaths annually in the United States than cancer of any organ save the stomach. For the younger age groups from five to nineteen, appendicitis is found to be uniformly one of the agents of death which exacts a high toll. Table 19, from a Massachusetts compilation (1936), discloses that appendicitis was the second to the fifth most important cause of death during these years.

Table 19.—Leading Causes of Death in Certain Age Groups in Massachusetts†

1–4 Years		5–9 Years	
Pneumonia	271	Automobile accidents	70
Tuberculosis	57	Pneumonia	64
Ear, nose and throat disease	49	Appendicitis	47
Automobile accidents	48	Heart disease	47
Appendicitis	43	Ear, nose and throat disease	43
10–14 Years		**15–19 Years**	
Heart disease	65	Tuberculosis	121
Appendicitis	44	Heart disease	75
Pneumonia	37	Pneumonia	53
Automobile accidents	37	Automobile accidents	53
Drowning	32	Appendicitis	42

Whereas the greatest frequency of the disease is during these years, the percentile mortality continues over a number of years (Fig. 111).

Among all causes of death at all ages appendicitis ranks next to syphilis, including all forms of that disease. Whereas the economic burden of appendicitis does not weigh so heavily on society, in that its victim does not become a public charge, as is usually the case of the patient with dementia paralytica, yet appendicitis commands undoubtedly a toll of more useful lives. This is the more to be regretted since deaths from appendicitis are avoidable if operation is undertaken early. The mortality is essentially due to procrastination. And whereas the lay public may feel that improvements in surgical technic may readily make adequate amends for this loss of opportunity, physicians know very well that their accomplishment in the management of peritonitis is little better than it was at the dawn of the era of abdominal surgery. Whereas the lives of more patients with neglected disease may be salvaged by conservative management, the only way to stop this wanton sacrifice of lives is to have patients with acute appendicitis come to operation early.

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* Averages of annnual death rates per 100,000 by color, sex and age (from one to seventy-four years).

† Annual average number of deaths, 1931–1935.

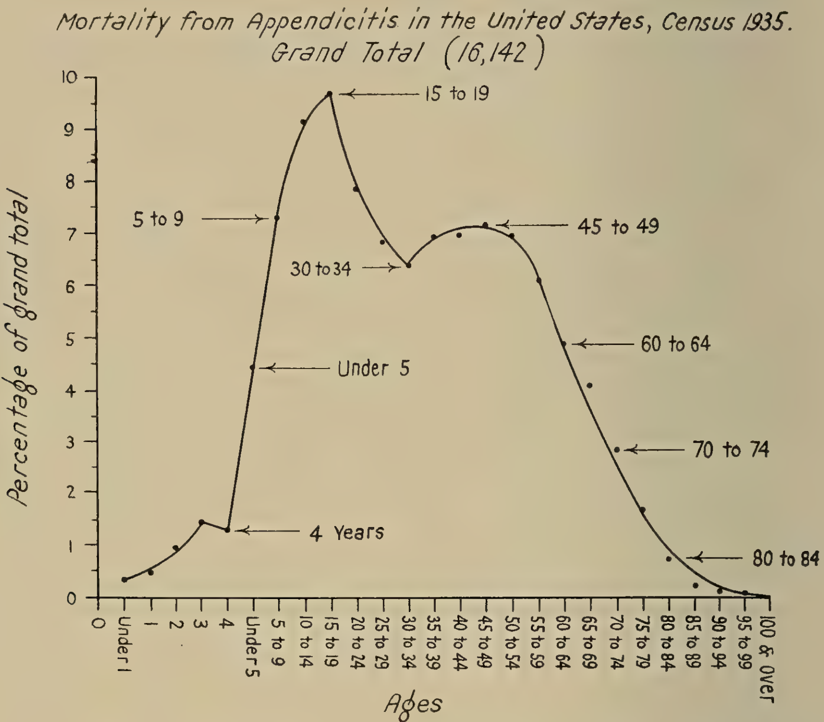

FIG. 111.—The plotted mortality curve of appendicitis by years in the United States in 1935. The highest mortality is between the ages of fifteen and nineteen, when 10 per cent of all deaths occur. It is to be noted, however, that at least 7 per cent of all deaths occur in each succeeding four year period until the middle fifties are reached.

The entire medical profession must be alive to the potential danger of this sword of Damocles which hangs over the head of every one who retains his vermiform appendix. A public health program of instruction must be undertaken to acquaint communities at large with the hazards of appendiceal obstruction. Mothers must be enjoined not to give cathartics in the presence of abdominal pain. Patients must be instructed not to treat themselves or consult their pharmacists but to see a physician for abdominal pain, and shortly after its onset. School nurses as well as physicians must learn that the absence of fever does not militate against appendicitis when abdominal pain is present. And, finally, the alleged health-restorative power of cathartics must not be broadcast over the radio or proclaimed by the pharmacist over the counter.

It is decidedly discouraging to contemplate, however, that among gainfully employed men between the ages of fifteen and sixty-four Jessamine Whitney (1934) found by a study of the mortality of ten states from the mortality stastics of the United States Census that the death rate for the group as a whole was 20.7 per 100,000, while for physicians and surgeons it was 22.1. Nowhere is the proverb of "physician heal thyself" more applicable!

The Frequency of Appendicitis.—The studies of Aschoff (1908) on necropsy material indicated that of persons dying in the sixth and seventh decades of life, 75 to 80 per cent exhibit evidence of previous disease in the appendix. Few persons who live the biblical three score years and ten reach the grave with a normal appendix.

Kraft (1929) found that about 2 per cent of Denmark's 3,500,000 persons surrender the appendix to the surgeon yearly. Barnes (1938) estimated that somewhat more than 1,500,000 persons (1.18 per cent of the total population) undergo appendectomy yearly in the United States. He expressed the belief that half again as many more should have had appendectomy. Kraft expressed the opinion that about 10 per cent of persons during their lifetime have at least one acute attack of appendicitis. Of those who recover spontaneously from an attack, he estimated the recurrence rate of attacks at 30 per cent. In his group appendicitis was as frequent in the female as in the male. R. E. Buirge, my associate, found that of a group of more than 27,000 persons, comprised of school children, nurses, men in CCC camps and patients admitted to the University of Minnesota Hospitals, 8.6 per cent had had appendectomy. The lowest incidence, 2.5 per cent, was among school children, and the highest, 28.7 per cent, among a group of 150 nurses. In a statistical study of appendectomy in the CCC, Rudder (1938) found the incidence of appendicitis in a group of 200,000 young men between the ages of eighteen and twenty-five to be 3 per 1,000 per annum. Wevill and Wallace (1933) estimated on the basis of the population of Scotland and an analysis of 8,000 cases of acute appendicitis observed over ten years at the Royal Infirmary at Edinburgh that the maximal incidence of the disease for the male is at twelve years and for the female about eighteen years. One in 200 (500 per 100,000) boys of twelve years were appendectomized annually for acute appendicitis, and 1 girl out of every 230 at the age of eighteen years. Gundel and Mayer (1934) have discussed interesting aspects of the appendicitis problem of Germany.

Alleged Seasonal Occurrence of Appendicitis.—A seasonal incidence has been claimed by a large number of writers, particularly those who insist on a causal relation between infection of the upper part of the respiratory tract and appendicitis. That infection may cause swelling of the lymphoid tissue, which in turn may obstruct the lumen of the appendix, has been admitted readily. Appendicitis during the eruptive fevers of measles and scarlet fever is by no means rare. Bowers (1938) was unable to detect any suggestion of seasonal prevalence of appendicitis in his group of cases. In the series of Wevill and Wallace seasonal occurrence was denied. A study of the mortality of appendicitis in this country from month to month lends no support to the belief.

Rostowzew (1906) was unable to establish any correlation between the occurrence of appendicitis and influenza in St. Petersburg. Renn (1916) came to the same conclusion with reference to tonsillitis and appendicitis.

Bowers (1942) has reported recently the occurrence of appendicitis in young soldiers receiving typhoid inoculations—occasioned presumably by swelling of the lymphoid tissue of the appendix.

NECESSITY FOR REVISION OF THE CLINICIAN'S CONCEPT OF APPENDICITIS

Whereas there may be other causes of appendicitis, the only one definite tangible agency which will bring about the sequence of events which terminates in diffuse leukocytic invasion of the walls of the appendix, gangrene or perforation is obstruction. As all the histologic varieties of the disease recognized by the pathologist can be reproduced by occlusion of the lumen in man or in animals (chimpanzee and rabbit) in which the appendix secretes fluid actively; it is reasonable to consider appendicitis as the sequel of luminal obstruction.

Hence, it is necessary to resurvey the symptoms and physical findings which are regarded generally as typical. Those specified by Murphy, pain, nausea and vomiting, abdominal sensitiveness, fever and leukocytosis, have been accepted almost universally as the clinical manifestations of the disease. The teachings of the late Sir David Wilkie (1931) with reference to "appendicular obstruction" should properly be applied in all cases of suspected appendicitis in the light of the significance of luminal obstruction in the bringing about of various end-effects of the disease. On the basis of the physical findings one can foretell the secretory capacity of an obstructed appendix no more accurately than the progress of the disease.

So far as appendicitis is not an infection primarily, the inflammatory features of the disease are usually absent altogether in the beginning. The pulse rate, temperature and leukocyte count may all be fairly normal for some time after the onset.

Appendicitis is essentially a closed-loop obstruction in which a very short segment is concerned, with no interference with continuity of the main intestinal channel. The only early findings in a closed-loop obstruction are intermittent crampy pain and local tenderness. Vomiting may be absent altogether. Elevation of the temperature, hurrying of the pulse and leukocytosis are evidence that the infective character of the disease has been set in motion.

It is as necessary that the physician reorient himself in the subjective and objective findings of the disease as that the pathologist revise his concept of appendicitis. The potential hazard of all closed-loop obstructions needs no amplification.

NEED OF REVISION OF INDICATIONS FOR EXCISION OF THE VERMIFORM APPENDIX

It is apparent that sacrifice of the appendix should be made on lesser indications than customary at present. If all persons in the upper brackets of life who exhibit evidence of previous appendiceal disease (75 to 80 per cent, according to Aschoff, 1908) actually were threatened at some time during their life by an acute attack, there might appear good reason to establish a new surgical covenant, and unlike that of circumcision contracted with Abraham, one binding on both sexes. No good evidence now available, however, indicates that all persons whose appendixes reveal traces of disease have actually suffered from appendicitis. The surgeon sees over himself the threatening shadow of the pathologist, who is accustomed to think in terms of morphologic rather than functional disturbances. In consequence the surgeon has become hesitant in excising the appendix on the lesser indications, though he knows very well that no constant correlation exists between a clinical appraisal of the severity of an attack and the progress of the process in the appendiceal wall. Reports like those of Charles W. Mayo (1934) and Rea and Kleinsasser (1938) are reassuring. In patients not admitting acute attacks but complaining of right lower quadrant pain in whom examination excluded other palpable causes, appendectomy was followed by relief of pain in 70 per cent of Mayo's cases and in 78 per cent of Rea and Kleinsasser's. Sources for abuse and disappointment in promiscuous appendectomy are obvious. The very occurrence of the occasional "adhesion-former," who is started on a life of chronic invalidism by excision of a fairly innocent appendix, constitutes a serious deterrent to operation without good indications. Nevertheless, physicians and surgeons must be less restrained in their indications for operation when symptoms suggest acute appendicitis. Marsch (1922) and Aschoff (1908), analyzing independent data, suggested that the mortality from the medical management of acute appendicitis is somewhere between 6 and 7 per cent. Surgeons with alert and knowing consciences are not likely to advise operation without just cause.

Those who affect to believe in the inheritance of acquired characters may be at pains to state that the removal of the appendix through a few generations might succeed in the anatomic elimination of this useless member. However, the covenant of circumcision, kept faithfully since the time of Abraham save for the dereliction of Moses in the wilderness, after which it was renewed promptly by Joshua, has failed to produce a race of male infants without a prepuce. And Matthew enumerated forty-two generations alone between Abraham and Christ! Unfortunately, therefore, there appears to be no safe method of promise other than surgical intervention for eradicating the dangers of an obstructed vermiform appendix.

WHAT IS CHRONIC APPENDICITIS?

If an appendix is removed a short time after an attack of appendiceal obstruction in which a diffuse suppurative process involved all the walls of the appendix, the excised specimen may exhibit evidences of healing. This may be mistaken for a chronic inflammatory process. Chronic appendicitis is essentially a loosely employed clinical designation for recurrent or persistent appendiceal obstruction. It is unlikely that a chronic inflammatory process exists in the appendix apart from specific granulomatous infections, such as tuberculosis, or the occurrence of chronic intussusception. The obliterative changes observed with increasing age are not wholly understood. Ribbert (1901) considered them physiologic; however, the normal ureter after nephrectomy retains its lumen. An ulcerative process usually destroys the mucous lining of a duct or tube and is also the likely antecedent of luminal obliteration in the vermiform appendix.

It has been demonstrated that the best determinant of whether the appendix will secrete is the presentation of a normal mucosa. Appendixes with atrophic glands and encroachment on the lumen by connective tissue proliferation failed to secrete. The more normal the appendix, therefore, the more hazardous is luminal obstruction. An obliterated appendix may withstand luminal obstruction apparently without hazard to its owner.

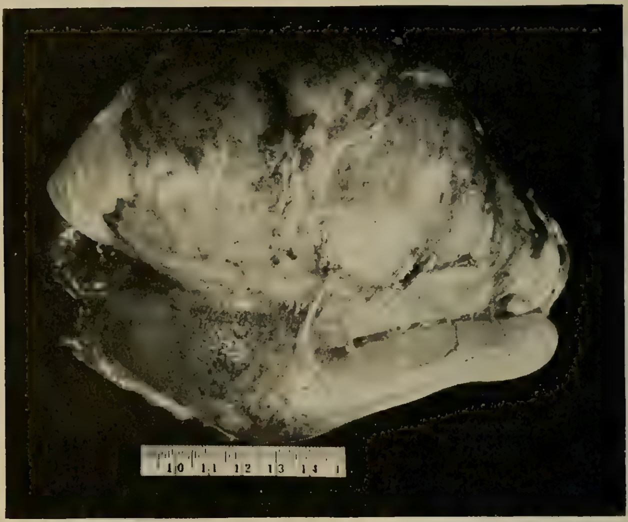

Fig. 112.—Mucocele after ligature of the cecal appendage in the rabbits.

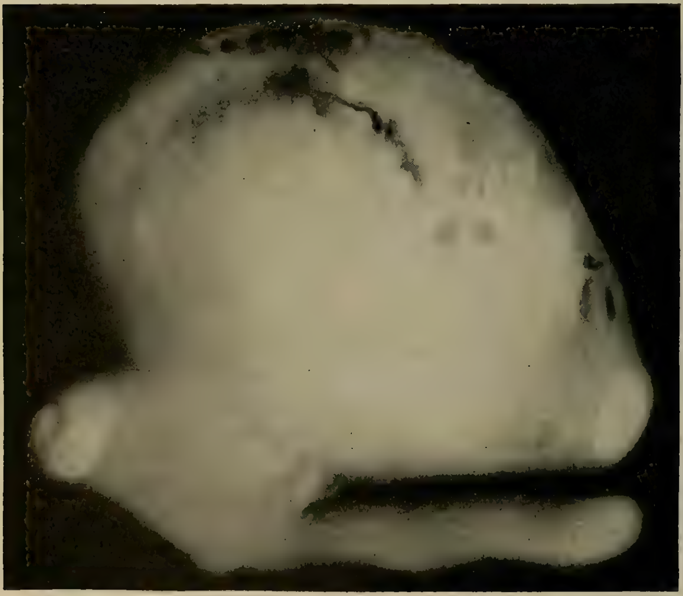

Fig. 113.—*X*-ray picture of mucocele shown in figure 112. The communication between the cyst and the appendage is wide (perforation with sealing).

MAY TRAUMA CAUSE APPENDICITIS?

Undoubtedly trauma may cause the appearance of histologic effects of inflammation, as in any other tissue, for inflammation is but the reaction of tissue to injury. There is no evidence, however, that trauma *per se* may give rise to appendiceal obstruction—the usual cause of appendicitis. That severance of its mesentery or transection of the appendix by trauma may give rise to a serious appendiceal disorder is obvious. These effects, however, are not to be confused with the alleged role of trauma in initiating spontaneous appendicitis, for which there appear to be no factual data.

THE RELATION OF THE VERMIFORM APPENDIX TO DISEASES OF OTHER VISCERA

Moynihan described "appendix dyspepsia," by which he meant to infer that diseased appendix may provoke symptoms referable to the upper reaches of the gastrointestinal canal. Braithwaite (1923) went so far as to suggest that the flow of lymph from a diseased appendix to the juxtapyloric lymph nodes may be responsible for the origin of both duodenal and gastric ulcer as well as gallbladder disease. He said that at operation, from inspection of the gastric outlet, one may diagnose with certainty the presence of a diseased appendix before it is seen. The criteria on which this inference is predicated are these: (1) pyloric spasm, (2) pyloric congestion and (3) enlargement of the lymph nodes along the distal margin of the greater curvature of the stomach. Recently Braithwaite (1942) described the occurrence of the ileogastric syndrome manifested by a group of symptoms accounting for the findings just enumerated.

All this, as far as one can know, is mere rationalization. There exists no factual proof that diseases of the appendix in the absence of suppurative complications may give rise to disease in other abdominal viscera. Coincidental excision of the vermiform appendix during the course of an abdominal operation needs no such justification. The potential hazard of a normal appendix to its owner is justification enough.

MUCOCELE FORMATION

It would appear from experiments on the cecal appendage of rabbits that the development of a mucocele is a fairly common sequel of appendiceal obstruction (Naeslund, 1928; Wells, 1937). The observation of my associate Dr. Richard L. Varco suggests that the visual antecedent is perforation attending luminal obstruction, followed by a sealing-off process. A fairly large communication can be demonstrated usually between the cecal appendage and the para-appendiceal sac (Figs. 112 and 113). Rupture of such a mucocele may in turn give rise to the process called pseudomucinous peritonitis. It is not likely, however, that the papillary tumor implants in the peritoneum, seen in ovarian cysts and occasionally described in cysts of the appendix, have such an origin. This latter occurrence in all likelihood is a neoplastic process. Such cysts, as well as carcinoid tumors and adenocarcinoma, may be seen in the appendix.

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CHAPTER XXVI

FUNCTIONAL DISTURBANCES OF THE COLON

GENERAL CONSIDERATIONS

Normal Bowel Function.—Before attempting a description of abnormal function, a working knowledge of the normal function is desirable. The motor transport through the digestive tract proceeds independently in each of its component segments. Thus, the esophagus empties a single mouthful in about eight seconds; the stomach empties a standard opaque meal in about five hours, the small intestine within four hours and the colon in from forty-eight to seventy-two hours. The manner in which the colon propels its contents is not yet entirely clear. In the proximal segment, which includes the cecocolon and the proximal part of the transverse colon, there is said to be an alteration of propulsion and retropulsion, at least in animals.[9] This has not been observed roentgenologically in normal man.[17] An important function of the proximal part of the colon is water absorption. In the distal portion, the progress is exceedingly irregular, long periods of quiescence—lasting hours—being interrupted by sharp peristaltic rushes called "mass peristalsis," lasting a few seconds and advancing the fecal column over many inches of bowel length. Owing to the rarity of these active periods in the normal bowel, they are not often seen roentgenologically, but in the irritable colon they are much more frequent. The roentgen appearance of these rushes was originally described by Holzknecht,[16] Hurst,[17a] Barclay[2] and Case.[10] The haustra remain well demarcated in the quiescent phases, but disappear completely with the formation of a sausage-shaped bolus at the head of the advancing column of a peristaltic rush. After the passage of the mass peristalsis, the bowel rapidly resumes its normal haustrated appearance. It is possible that peristaltic rushes accompany phases of increased intracolonic tension, such as occur after discharge of the gastrocolic reflex. According to this reflex, passage of food through the pylorus causes entry of ileal contents into the cecum, thus increasing the pressure within the large intestine. This is in keeping with the observation that peristaltic rushes are more frequent in the morning and after the passage of a wave down the small intestine.[35]

As already implied, the contents of the cecocolon are fluid, whereas those of the distal portion are formed into a soft fecal column. As the column progresses distally, the processs of dehydration continues, so that by the time the rectum is reached the consistency normally favors complete and easy evacuation. The haustra are believed to aid actively in dehydration. The exact consistency of the normal feces depends on a rather delicate balance between the amount of food residue, represented almost entirely by vegetable and fruit fiber, and the degree of dehydration, which in turn depends on the rate of progress through the large intestine. When this balance is normally struck, the resulting stool contains from 70 to 85 per cent water[39] and is formed of sausage-like segments. These are produced by the molding of the fecal column in its passage through an actively relaxed anal sphincter. The amount of the stool represents the contents of the rectum and of the entire pelvic colon, and often that of the iliac and the descending colon as well. The weight of the average normal wet stool on the standard Schmidt diet is 250 Gm. ($\frac{1}{4}$ pound).[40]

When the balance just described is disturbed, as in colonic malfunction, the resulting stool departs from the normal in bulk and consistency. With hypermotility, the stool is larger and softer and becomes mushy or watery. It may be accompanied by products of mucosal irritation, such as mucus, or of mucosal damage, such as pus or blood. With constipation, the stools are small and dry if passed. If the stool is retained, dehydration continues so that the weight of such a retained stool becomes practically *nil.* This accounts for the failure of the subject to gain weight rapidly during periods of constipation, a fact which seems a great surprise to the laity.

In the normal person, the entire passage through the colon to the rectum is accomplished without sensation. Sensation comes into play in the filling of the last portion of the tract, the phenomenon thus produced being known as the defecation reflex. This sensation is the result of the sudden unloading of the pelvic colon across the angulated pelvirectal flexure into the rectum. In the normal state the rectum is sensitive to such rapid filling *en masse,* and the pressure phenomenon so produced results in a more or less urgent call to stool. The most prominent component of this call is the familiar lower abdominal cramp, but sometimes remote sensations are produced—such, for example, as hyperesthesia or paresthesia of the thigh or left forearm and hand. Under certain abnormal conditions, filling of the rectum is not accompanied by discharge of the defecation reflex, and this leads to rectal constipation, which will be described later.

CONSTIPATION

Definition.—Constipation implies functional impairment in the inherent capacity of the colon to produce normally formed stools at regular and sufficiently frequent intervals. Normal completeness and ease of evacuating the rectum and lower part of the pelvic colon are lacking. The absolute frequency of bowel movement depends chiefly on the type of diet, vegetarians often moving their bowels two or even three times a day. For most persons one stool a day is normal. Judged by roentgen standards, constipation may be diagnosed when the total colon emptying time after a standard barium meal exceeds seventy-two hours. Combining all these concepts, constipation may be said to exist when the inherent capacity of the colon fails to produce normally formed stools at regular intervals, usually once daily, or when the rectum is evacuated with difficulty or when the total colon emptying time exceeds seventy-two hours, as judged by the usual *x*-ray criteria.

Incidence.—Constipation is the most common of all disorders of digestion. It was noted 2,261 times in a series of 5,000 private patients, an incidence of 45.2 per cent. Women are slightly more inclined to constipation than men (55 to 42 per cent) and brown-eyed persons more than blue-eyed (47 to 44 per cent), as determined by a survey of 1,000 consecutive persons in each group. The incidence figures vary according to whether the diagnosis is made from the history or from the roentgen study of a progress meal. This point was investigated in a group of 844 cases. Agreement between the history and the roentgen findings was noted in only

68 per cent, as shown in the table. In other words, more people think they are constipated than are (20 per cent), and a small number (12 per cent) are actually constipated who do not suspect this condition.

TABLE 20. COMPARISON OF HISTORY AND ROENTGEN FINDINGS

	Cases	Percentage
Agreement between history and x-ray	569	68
Disagreement between history and x-ray	275	32
Constipation by history—x-ray negative	169	20
Constipation by x-ray—history negative	108	12

Constipation usually begins in youth unless it is of the reflex, or secondary type. In 86.5 per cent of the women and in 72.5 per cent of the men in Thaysen's[44] series, constipation of the "habitual" type became installed before the age of twenty-six.

Etiology.—The etiology of constipation is complex, many factors being responsible. The chief causes may be enumerated as follows:

1. **Anomalies of the Colon.**—The most important of these is the redundant colon,[23] which occurs in 22 per cent of constipation cases, about one and one-third times its general incidence. Conversely, over two-thirds (72 per cent) of patient with redundant colon are constipated. The reason for this high incidence is not only the greater time required for passage through the increased bowel length, but the frequency of spasm proximal to the site of the redundant loops. A closely allied anomaly is a congenital kink of the pelvic colon, which seems to predispose to delayed transit in this particular region. The role of pelvic colon redundancy in the production of rectal constipation will be discussed later.

Conversely, short colons usually empty rapidly. Thus, with short colon associated with high cecum, constipation occurs about half as often as with redundant colon (37 per cent *vs.* 72 per cent).[22]

2. **Body Habitus.**—Owing to the lowered muscular tone in asthenic as compared with sthenic persons, constipation is more common (50 per cent *vs.* 42.2 per cent) in the former group. Possibly the tendency to spasticity in stocky persons tends to keep up the incidence of costiveness in the sthenic type, thus offsetting somewhat the effect of the generally increased smooth muscle tone in the group.

3. **Diet.**—Dietary factors responsible for constipation are of several varieties. Perhaps first comes insufficient water drinking. Next, it should be obvious that irregularities in meal hours, varying amounts taken at corresponding meals and occasional omission of meals will sooner or later throw out of order the regular habit of bowel movement. "No regular food intake, no regular stool output" may well be a health rule. Another fault is general food restriction from fads and especially phobias. This is of considerable practical importance, since no matter what the primary digestive trouble may be, food restriction, be it from fear of food (sitophobia) or fear of eating (phagophobia), is a common accompaniment, with the result that constipation develops from insufficient bowel stimulation.

The foodstuffs generally considered responsible for the stimulus to bowel function are fats, fruits, vegetables and coarse cereals. To produce normal daily evacuation, the diet should contain residue equivalent to a daily fiber intake of 90 to 100 mg. per kilogram of body weight.[12] In addition to their high vegetable fiber content, fruits contain cathartic sugars, acids and salts. The fats act mechanically both as lubricants in the neutral state and as mild irritants in the form of split fats.

4. **Psychic and Nervous Factors.**—Agitation, restlessness, hurry and the grosser emotions of anger, fright and anxiety are well known causes of constipation. The early morning rush associated with business, school and office is responsible in many cases. The diarrhea of fright is well known, but in my opinion the constipation of fright is far more common. On the other hand, even mild excitation, such as that associated with travel and change of environment, is a potent cause of constipation in susceptible persons. The neurogenic element in the etiology of constipation has been well described.[6]

One of the peculiar facts in connection with constipation is the concern with which some persons regard their failure to secure a daily bowel movement. Not only may an occasional omission be perfectly explicable on the basis of some of the causes just mentioned, but it may even be regarded as well within normal limits if it is not associated with physical discomfort or disability. Unfortunately, in these apprehensive persons only too often either a vicious bowel habit or an apprehension neurosis or both conditions develop.

Fatigue may also be considered under this head. A sufficient degree of general bodily rest and relaxation is essential to the proper functioning of all the organs, and the bowels form no exception to the rule. Whether or not the fatigue products of metabolism are actually constipating, it is certain that in many cases costiveness is associated with insufficient rest and particularly with insufficient sleep. This is often the case with those who work at night.

5. **Endocrine Factors.**—T. R. Brown[7] clearly described hypothyroidism as a cause of intractable constipation. The patients were chiefly women in the fourth to the sixth decade of life. The basal metabolic rate was between − 10 and −19 per cent.

6. **Associated Organic Digestive Disease.**—In some cases, the presence of appendiceal or gallbladder inflammation or other organic disease may be responsible for constipation. The bowel stasis in these cases is reflex and apparently spastic.

7. **Viscious Habit Formation.**—Perhaps the greatest perpetuating cause of constipation is vicious habit formation, too often the result or accompaniment of poor home discipline and inadequate youth training, with resulting neglect of the call of nature because of preoccupations, laziness or embarrassment. To this should be added the uninviting condition of toilets in the poorer types of schools, shops, farms and tenements—conditions that demand remedy at the hands of the appropriate social, educational or administrative authorities.

Once the chain of regular bowel evacuations is broken, once the fecal stasis begins to cause discomfort, it is but a short step for the sufferer to seek artificial methods of relief. He embraces thenceforth either the cathartic or the enema habit or both, and his constipation bids fair to remain fixed for life. Physicians have not been without blame in this matter. A prescription for a cathartic, no matter how well fitted to the temporary needs of a patient, may be just as persistently used as any patent medication, particularly after an operation or childbirth. In such cases the surgeon or the obstetrician just seems to forget to tell the patient that the artificial bowel aid is but temporary and that normal, spontaneous bowel function must be restored at the earliest possible moment.

Irrigations are often prescribed for some special reason, such as the relief of various real or imaginary toxemias or metabolic disorders. Permissible as such therapy may be for the purpose intended, it should nevertheless be borne in mind that the results achieved are always at the expense of the bowel stability and the bowel reserve. Here again a *restitutio ad integrum* should be insisted on as soon as the need is over.

Varieties.—Although several varieties may and usually do coexist, it is helpful to describe separately the following types of constipation: atonic, spastic and rectal, that accompanying redundant colon and that associated with mucous colitis.

1. **Atonic Constipation** is the form usually present in asthenic, malnourished persons. In some cases a congenital intestinal atony or hypoplasia is assumed to exist. A much more important practical cause is the long-continued use of cathartics or enemas. These tend definitely to weaken the smooth muscular tonus, and in extreme cases result in a complete decompensation of colon function. The most extreme atonic constipation that I have observed has occurred in elderly depressed women. Some observers, notably Alvarez,[1] have expressed the belief that the division into atonic and spastic varieties is no longer justifiable, as spasticity seems apparent in all cases of constipation. This is true if one relies only on x-ray studies following the barium meal. However, I believe—and in this I am supported by the careful observations of Larimore[29]—that an atonic colon is accurately revealed by observations after an opaque enema. This type of investigation shows much dilatation as well as increased capacity when the colon has become decompensated. The "postural tone" of the large intestine as so revealed speaks clearly for atony rather than for spasticity.

2. **Spastic Constipation.**—Schwartz[41] described this as "dyskinetic constipation," to indicate the irregular, difficult and painful progress of the colonic contents. It is the most common variety, often combined with other forms. The distal part of the colon is the site of increased tonus, either from the hepatic flexure onward or more particularly in the iliac and pelvic portions. The proximal part of the colon may be correspondingly dilated, the cecum, ascending colon and at times the transverse colon acting as reservoirs for large accumulations of feces which are passed, small portions at a time, beyond the contracted areas. In such cases there may be daily but insufficient evacuations, or, particularly with reflex involvement, the bowels may not move for several days—up to a week or more—at a time.

The common symptoms are abdominal cramps or sticking pain, generally localized in the left lower quadrant and usually increased by physical exertion and by catharsis or enemas; belly consciousness, as in irritable colon, and the passage of small hard and lumpy stools. These distinctive feces resemble small balls or pellets like sheep droppings, the term "sheep-dung stools" being used to describe the condition. Palpation of the left lower quadrant reveals a tight and tender iliac colon, the "corde iliaque" of French writers. On the opposite side of the abdomen, the cecocolon may be found to be distended, gurgling and similarly tender, but less so in degree. The anus may feel tight to the examining finger. Inspection of the pelvic colon with the sigmoidoscope often reveals irritability and spasm which may prevent the introduction of the whole length of the instrument.

3. **Rectal Constipation (Dyschesia).**—In some cases the stool packs in the rectum, and this organ is almost always found filled with feces. This variety of constipation was encountered in 18 per cent of the 844 cases in which the emptying of the colon was studied roentgenologically after the administration of a standard barium meal. In all these cases there was no delay in the progress of the stool through the proximal part of the colon. Indeed, in some cases this progress seemed accelerated. The barium usually began to accumulate in the rectum at twenty-four hours and was fairly hard and impacted by forty-eight or seventy-two hours, the bowels not being moved in the meantime.

There seems to be several distinct causes for the development of dyschesia. The first was well presented in the original description of this condition by Sir Arthur Hurst:[17a]

> The habitual neglect of the call to defecation leads to the accumulation of the feces in the rectum and pelvic colon which become . . . distended. The distention diminishes the tone and impairs the contractility of the musculature. . . . The weakened muscular coat is incompetent to do its work, and, even if a greater effort be made, the evacuation remains incomplete.

Marked involvement of this type is cometimes encountered in older bedridden or paralytic persons, a point to keep in mind if one is responsible for the care of the aged. In such patients a mild form of intestinal obstruction may occur, but surgical intervention may be avoided if the real nature of the trouble is appreciated.

A second well known cause of dyschesia is the presence of any condition which causes pain during defecation, such as inflamed or thrombosed hemorrhoids, and fissures or pelvic peritonitis. This type not infrequently follows childbirth.

A third variety not at all well known, but in my experience by no means uncommon, is associated with redundancy of the pelvic colon. In this condition the redundant loop acts as a barrier which prevents the filling of the rectum with the speed and the bulk necessary for the adequate discharge of the defecation reflex. The small amount of stool that spills over the redundancy seems to accumulate in the rectum entirely below the threshold of consciousness. Thus a silent impaction gradually develops.

4. **Constipation With Redundant Colon.**—With congenitally increased colonic length the large intestine undergoes considerable looping or reduplication. This is the most common anomaly of the colon, occurring 343 times in 1,850 consecutive x-rayed patients.[23] Constipation in these patients usually dates from birth. It occurs in over two-thirds (72 per cent) of all cases of redundancy; conversely, redundancy occurs in over one-fifth of the cases of constipation. The constipation of redundant colon is characterized by unusually long intervals, sometimes as long as one week, between stools, and by difficulty in expelling enemas, which become "lost" in the abdomen.

Gas distress is sometimes striking. Both general and localized distention occur, the latter often corresponding precisely to the redundant loop. If the splenic flexure is placed high in addition (so-called diaphragmatic flexure), characteristic pressure effects result from the imprisonment of gas under the left side of the diaphragm. These pressure phenomena may affect the heart, causing anginoid pains and pulse irregularities; when the pressure is against the stomach, heartburn, fulness or belching may follow.

Pain is also likely to be present somewhere in the abdomen, owing to superimposed spasm proximal to the point of redundancy, and may be associated with colonic irritability, especially in victims of the cathartic or enema habit. According to their location, the pains may suggest carcinoma or diverticulitis of the colon, heart disease, gallbladder disease or appendicitis.

5. **Constipation With Mucous Colitis** will be discussed in the section on unstable colon.

6. **Proximal Colon Stasis** is not, strickly speaking, a form of constipation at all, because in constipation the delay affects primarily the distal part of the colon. Stasis in the cecum or cecocolon does not of itself cause disorders of clinical significance.[28] However, with stasis in the presence of constipation plus a low-placed cecum (hyperdescent of the cecum), there are headache, vomiting and right lower quadrant pain and tenderness. Their incidence is almost twice as great with the low cecum as with normal or high cecum. The mechanism of their production is obscure. The treatment is that of low cecum.

Symptoms.—The symptoms associated with constipation vary greatly in different persons. The local symptoms have been mentioned in the description of the various varieties of constipation, namely, mild pains due to spasm, especially in the left iliac fossa; belly consciousness due to gas retention, or packing and heaviness in the rectum or perineum due to dyschesia. Secondary local results associated with the passage of hard stools are inflammation of the anal crypts (cryptitis), hemorrhoids and fissure *in ano*, causing the appearance of bright blood on the stool or toilet paper.

Many patients attribute various systemic complaints to constipation. Among these symptoms are, in order of their importance, a feeling of "poisoning," "intoxication," inertia or lassitude, headache, nausea, regurgitation, fulness immediately on eating, bad breath and coated tongue. When referred to as a group, these disturbances are often called "autointoxication" or "biliousness," and their nature has been the subject of much speculation. Alvarez[1] expressed the belief that most of these sensations are the effect on consciousness of the reversal of the intestinal gradient in sensitive persons. This reversal results from nerve impulses that may originate as high as the cerebral centers. There also seems to be some evidence that these symptoms are more likely to be due to a combination of proximal colon stasis with constipation than to constipation alone, which affects the distal part of the colon.[28] That symptoms of biliousness may be due to some form of liver insufficiency has received its chief support from the apparent beneficial effect of bile salts or other cholagogs. Calomel and other cathartics also control these symptoms. However, Alvarez stated the opinion that when cathartics relieve biliousness, it is simply by restoring the downward current. Again, it is possible that many of the symptoms attributed to constipation may be brought about by the remedies used to treat the condition, through the irritation of absorbing mucosal surfaces and the hastened transport of incompletely elaborated intestinal contents. In any case, long periods of constipation have been undergone by many persons without any systemic effects whatever. The old theory of intestinal (protein) intoxication has been recently well presented by Bartle.[4] That constipation may result in serious organic disease, such as cancer, has been claimed by some, notably by A. C. Jordan.[18] I found no basis for this view as far as cancer is concerned,[26] and Alvarez and his co-workers[1] showed that constipation is in no way responsible for high blood pressure.

Diagnosis.—The diagnosis is usually made from the history. This may reveal a laxation rate of less than one per day, or the stools may be described as small, hard and difficult to pass. However, in some cases of cumulative constipation, the history is misleading because a daily stool is reported, and the true condition of insufficient evacuation can be revealed only by roentgen study. In such cases the *x*-ray reveals a prolonged total colon emptying time.

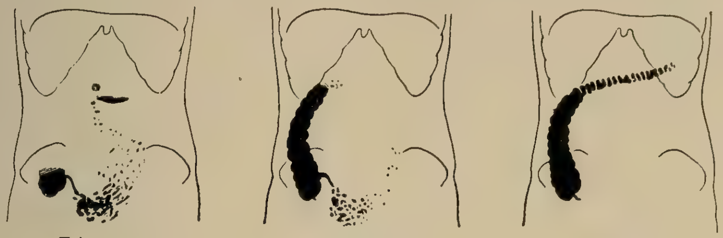
Physical examination in cases of spastic constipation may reveal the presence of a spactic and sensitive colon which can be rolled like a hard cord in the left iliac fossa. In rectal constipation, palpation with the finger will reveal the ampulla full of scybala, the patient being unconscious of the rectal packing in many cases. Those charged with the care of aged, bedridden or paralytic patients would do well to perform periodic rectal examinations.

Inspection of the stool itself reveals the diminished amount, the increased consistency with formation of scybala or pellets and the occasional evidence of mucosal irritation, such as streaks of blood or mucus.

Roentgen examination gives by far the most comprehensive information and should be used whenever possible. The ideal procedure is to administer a standard barium meal and follow its progress by daily roentgen observation until it is entirely eliminated from the colon.[24] During this period the patient is not hospitalized, but is encouraged to go about his business and maintain his usual environment. This should be carefully explained to the patient. A second rule is that during the entire period of observation, which lasts from at least three days to a week or more, the patient is forbidden the use of artificial aids to bowel function. Here one may expect to encounter considerable opposition from those addicted to cathartics, enemas or irrigations. As is well known, many patients believe that their bowels will never move if unaided, or that they will be 'poisoned'' if a day or more goes by without a bowel action. A good way to handle such patients is to assure them that sooner or later the bowels always move spontaneously, unless a rectal impaction develops, in which case it will be appropriately treated, and that nothing serious will happen even if they have transient discomfort for a day or two. This reassurance can be further strengthened once the examination is under way, by exhibiting each day's *x*-ray film as proof of the progress made by the barium column even when no bowel movement has occurred.

The next point to take up with the patient is the matter of diet. Many laymen believe that constipation is properly treated by food restriction. This idea must be uprooted, and the physician must insist that enough food be consumed during the period of examination to afford an adequate stimulus to bowel action. If the patient is weighed each day, one can quickly decide whether these orders are followed. In regard to what food to eat, I prefer to allow the greatest freedom of choice, within reasonable limits. This is done in keeping with the philosophy of leaving the patient as much as possible in his "natural habitat" during the observation period.

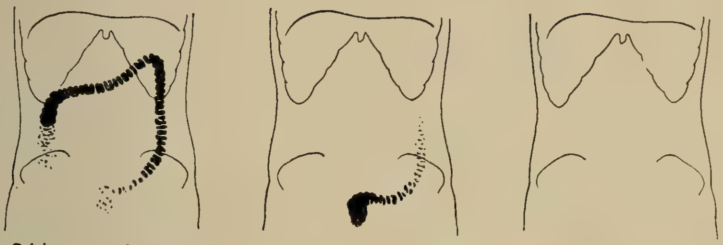
Finally, the patient is requested to keep track of the number of bowel movements, if any, from one day's roentgen observation to the other. If constipation is present, the patient is asked to try to move the bowels once each day, but is not permitted to "sit and strain" in order to do so.



3 hours
cecum beginning
to fill

5 hours
stomach empty

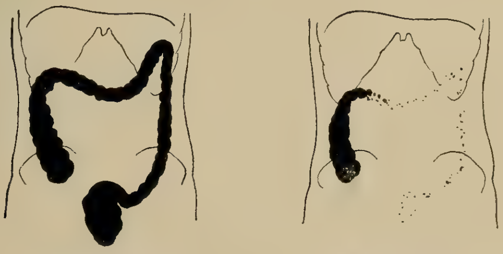
9 hours
small intestine
empty



24 hours - 1 stool
colon fairly well
filled

48 hours - 2 stools
only distal colon
filled

72 hours - 3 stools
colon and rectum
empty



Opaque enema

Enema after evacuation

FIG. 114.—Normal "time table" after progress meal and normal opaque enema findings. (Kantor, *Synopsis of Digestive Diseases*; courtesy of C. V. Mosby Company.)

As for the observer, he should always bear in mind the possibility that a rectal impaction may develop and should be prepared to prevent this. Although it is unlikely that the opaque meal can of itself initiate rectal impaction, it can certainly aggravate the condition when a tendency to dyschesia exists. When an impaction is encountered, it should be treated as described in the section on rectal constipation. Under normal conditions, the colon is empty of barium between forty-eight and seventy-two hours after the barium meal, with two to four spontaneous stools in the interval. Any delay beyond seventy-two hours, or the development of rectal impaction before this time, indicates the presence of constipation. For a time table showing the progress of the barium meal through the normal colon, see figure 114.

To complete the roentgen study, an opaque enema is administered, in order to study the topography of the colon as well as to appraise its postural tone. Normally 38 ounces is required to fill to the cecum. In the presence of redundancy or colonic atony, this amount may be increased to 1½ quarts or more. With spastic constipation, on the other hand, the amount is reduced to 32 ounces or less. The distal iliac or pelvic part of the colon is much narrower and the proximal part much wider than normal, the ratio being 1 to 3 instead of the usual 1 to 2.[11] In addition to the narrowing, the distal part of the colon is usually the site of considerable spasm, shown as increased depth of haustration.

Treatment.—The prophylaxis of constipation consists in the provision of adequate opportunity to move the bowels and in sufficient water drinking. In order for water to reach the lower bowel, it is best taken when both the stomach and small intestine are empty. This means that the water should be drunk the first thing in the morning. Regular meals and a balanced diet containing sufficient bulk are likewise important. As a result of an experimental study conducted with L. F. Cooper, it was estimated that the daily intake of 20 small prunes, 3 bananas or 2 apples, in addition to average amounts of vegetables and cereals, will supply the Cowgill requirement of stimulant in the form of food fiber.[27] Fats are also valuable in constipation.[42] Butter and olive oil are particularly useful. Most patients will take up to ¼ pound of butter daily if encouraged.

Visceroptosis and malnutrition should be treated by rest, abdominal support and a fattening diet. Intermediate feedings may be needed. Frequent and regular weighings are essential.

The psychic and nervous causes should be controlled by appropriate mental hygiene. This means, specifically, encouragement of the patient to believe in the ultimate restoration of spontaneous bowel function. Sufficient rest, especially sleep, should be provided, as well as adequate vacations and, in most cases, sedative medication. Cathartics, enemas and irrigations should be summarily discontinued. As these are habit forming, the withdrawal treatment in this situation presents the same psychic as well as physiologic problems and hazards as does the more heroic program in the case of drugs of the narcotic order. Courage, patience, strength and perseverance are required of the physician in both cases. To bolster the patient's morale and enlist his intelligent coöperation, an explanation of elementary colon physiology and hygiene is invaluable. This task is greatly simplified if it can be undertaken during the period of the roentgen study of colon function. There is no sounder psychotherapy for an apprehensive patient than demonstration by a series of x-ray films that the colon still propels its contents even in the absence of a bowel movement.

For the constipation of hypothroidism, thyroid extract has proved very effective. The dose, however, varies from ¼ to 6 grains per day and must be continued indefinitely when the condition is intractable.[7]

For atonic constipation the best treatment is the gradual addition of bulk to a basically smooth diet. Fruits are best, but in some cases artificial bulk producers are required. Among the most popular of these are agar, mineral oil alone or combined with agar, bassorin, psyllium seed as such or better still in powdered form (metamucil, mucilose), cellulose and bran. The dose is varied to suit individual requirements.*

Spastic constipation requires rest, sedatives, lubricants and antispamodics. The latter are best administered in the form of tincture of belladonna in increasing doses to tolerance (15 to 22 drops three or four times daily). Belladonna is particularly valuable when pain is present.* Oil may be administered by mouth or by rectum. Rectal administration will be described later. Those forms of spastic constipation which result reflexly from the presence of associated inflammatory or other organic disease require the removal of the primary condition (appendicitis, gallbladder disease, kidney stone, etc.) for permanent relief.

Rectal constipation is treated by local, as opposed to oral, measures. For the acute impaction, as in paralysis or after the administration of barium for roentgen diagnosis, the following procedure is recommended: After the insertion of an anesthetic suppository, the impaction should be broken up by the finger. A bulbful of oil should then be instilled and retained for fifteen to twenty minutes. After this a saline enema of $1\frac{1}{2}$ quarts should be administered. If the impaction persists in whole or in part, the entire procedure should be repeated. Old impactions, such as those encountered in paralytic persons, are handled in the same way in general, except that large irrigations may be required before the impaction is completely relieved.

In dyschesia due to local lesions (fissures, hemorrhoids), the latter should receive appropriate treatment. In chronic rectal constipation in general, a course of reëducation of rectal function is essential. This involves the nightly instillation of about 2 ounces of oil (corn oil or olive oil) by means of a small hard rubber syringe fitted with a hard rubber tip. Since the oil should be retained overnight, care must be taken to exclude air from the injection. In some cases, plain cocoa butter suppositories may be substituted or small water injections may be used in the morning in place of the oil at night. All these procedures should be continued for weeks or months and should be reduced only gradually as bowel function increases.

In spasm of the anal sphincter or in stricture following local operation or disease a course of anal dilations may be necessary. These may be accomplished either by stretching with the relatively soft Wales bougies or by the wearing of hard rubber dilators for increasing periods. These dilators come in various sizes and are available through surgical supply houses under the name of Dr. Young's rectal dilators.

Cathartics have no place in the routine treatment of constipation. Being habit-forming drugs, they increase rather than relieve the evil. Their use should be reserved for special occasions when purgation is required, as well as for the care of the very aged and for those suffering from certain acute and chronic conditions. If deemed of value for some ulterior purpose, it must be borne in mind that they accomplish their end only at the expense of weakening normal colon function. When cathartics are used, it is important to order the smallest possible effective dose, that is, the amount just sufficient to produce soft, formed stools. Watery stools are an indication that the dose is excessive.

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* Thiamin chloride in 3 to 7 mg. doses at mealtime has recently been shown to stimulate peristalsis, particularly of the colon. For patients with atonic constipation, prostigmin in small doses may be helpful, particularly for elderly and bedridden patients with no organic obstruction.—EDITOR.

* Atropine sulfate, in doses of $\frac{1}{200}$ or even $\frac{1}{150}$ grain *per os*, may be advisable. It has the added advantage of producing partial paralysis of the parasympathetic nervous system.—EDITOR.

The same general rules apply to enemas and irrigations. For bedridden patients, however, an occasional saline clysma will be found useful to relieve distention or overcome impaction. It is not always necessary to administer the injection daily. As soon as the patient becomes ambulant the enemas should be discontinued.

For the so-called intestinal autointoxication symptoms, good results are claimed for sodium ricinoleate. The drug is given in 5 grain capsules, the dose varying up to six capsules a day (Morris and Dorst[34]).

THE UNSTABLE COLON

(Irritable Colon, Spastic Colon, Simple Colitis)

Definition.—The unstable colon[21] is that which may show at various times, or in various parts at the same time, delay or hypermotility, atony or spasm. The condition is characterized by instability of function in the absence of an organic lesion and must be distinguished from true colitis, which is always associated with organic changes. The concept of the unstable colon includes both the "irritable" colon with diarrhea and the "sluggish" bowel with constipation, as well as the syndrome commonly described as "alternating constipation and diarrhea." The departure from the normal function may be entirely, or for long periods, in one direction, or there may be repeated oscillation from one extreme of malfunction to the other.

Incidence.—In its various forms colonic instability is one of the most frequent conditions encountered in civilian practice, occurring in 30[19] to 50[43] per cent of patients admitted to the gastrointestinal service. Of 3,000 private ambulatory patients with digestive symptoms, both constipation and colitis (unstable colon) were diagnosed in approximately 40 per cent.

Etiology.—The unstable colon may result from many factors. As in all functional disorders, nervous influence play a prominent role.[25] Probably the most important of these is a congenital generalized instability of the autonomic nervous system.[3] This is often hereditary and has been described as vagotonia, spasmophilia and sympathicotonia. Most neurotic and neurasthenic conditions seem to belong to this class. The colon may be the only organ affected, or the instability may involve other portions of the digestive tract or other systems as well. Occasionally an *acquired* localized instability may result from a cured organic disease, such as bacillary dysentery, when the related nerve pathways probably remain "sensitized" after the disappearance of the local organic condition.

Disorders of the psychic component of digestion may be responsible also for colonic malfunction and should be recognized by all practitioners. The patient's symptoms depend on his feelings or emotions or on certain perceptions or ideas which have, out of past experience, caused a conditioned reflex pattern. This mechanism may not be understood by the patient and may exist only in his "subconscious mind." With psychoneuroses (*e. g.*, the anxiety neuroses), symptoms of colonic instability are relatively frequent. These develop in sensitive persons in the face of insoluble personal problems. Anxiety hysteria is a common result of such conflicts. With severe psychoses, such as dementia praecox, circular mania and the paranoid states, digestive symptoms may occur early but are usually absent when the disorder is fully developed.

Constipation and especially the abuse of cathartics, enemas and irrigations aggravate and perpetuate colonic malfunction. Jordan found that 73 per cent of her patients give a history of such abuses. The tremendous hold these vicious habits have on the population is due not only to widespread advertising of laxatives but to popular misinformation. Thus, the average patient seems to believe: (1) that the retention of waste matter in the body beyond one day is detrimental to health; (2) that if the bowels fail to move one day he must do something about it; (3) that a large mushy stool or series of stools is normal and even beneficial; (4) that the colon is a sewer, to be emptied as often and as thoroughly as possible; (5) that the resting period of the bowel which follows a thorough purging is a sign of constipation which can be cured only by more purging; (6) that many common symptoms, such as headache, fatigability and vertigo, are best treated by cathartics or enemas.

People take cathartics not only because they are constipated but because they think they are constipated. Of 148 *x*-rayed cathartic users studied by me,[21] the colon expelled the barium meal on time in 39 per cent. Furthermore, of 530 patients with the cathartic habit, 6 per cent gave no history of constipation but used these drugs for headache, arthritis, pimples or general neurasthenia. However, no matter for what purpose these vicious habits are contracted, the result is always the same, a weakening of the autonomous bowel function and the development of increasing instability as time goes on. In addition, the nutrition suffers and hemorrhoids develop, the incidence of piles being almost one and one-half times as great in cathartic users as in the general run of patients.

Rough foods are responsible in some cases, and milk is particularly harmful, often increasing colonic irritability and in many persons producing explosive, sour defecations and troublesome flatulence, due, it is believed, to the elaboration of hydrogen gas in the intestine. Another way in which foods may upset colonic stability is by their anaphylactic action. Eyermann[14] has reported a case of colonic spasm, observed roentgenologically, apparently due to whole wheat bread, to which the patient was sensitized. It was relieved by the administration of 1 : 1,000 epinephrine chloride. The allergic origin of symptoms is especially stressed in mucous colitis (*q. v.*). The passage of native protein through the normal gastrointestinal wall has been offered as a possible explanation of anaphylactic digestive symptoms by Ratner and Gruehl.[35]

Organic colon disease, such as ulcerative colitis and cancer, or disease of adjacent digestive organs, such as the small intestine, gallbladder and appendix, may be associated with varying degrees of colonic instability, as may more remote lesions and diseases, such as those of the female pelvis, the urinary tract or the respiratory system.

Among other possible etiologic factors may be mentioned vitamin deficiency,[31] calcium deficiency[37] and bacterial subinfection, particularly with certain strains of colon bacilli.[32]

Symptoms.—Alternating constipation and diarrhea is perhaps the most common intestinal manifestation. Another frequent complaint is "belly consciousness," in which every movement of gas or feces, as well as every jar or pressure from without, is registered as a disagreeable experience in the over-sensitive abdominal nerve plexuses. A peculiar sense of goneness, weakness, sweating or even complete exhaustion or fainting immediately preceding or following a bowel movement is described by some patients. This phenomenon resembles a mild shock in particularly unstable persons. Urgent mushy or watery stools are easily set off by many factors that would not affect more stable persons. Menstruation may be cited as such a factor, for in my experience menstrual diarrhea is fully twice as common in women with colonic instability as in women with nonirritable colon (61 per cent *vs.* 26 per cent). Other causes for diarrheal outbursts are the ingestion of milk, icecream, cheese, cold drinks and other special foods by susceptible persons, fatigue and particularly emotional upsets. Mucus may appear in the stools. When this feature is prominent, the condition is usually spoken of as mucous colitis, which will be described later in more detail.

Actual pain is also common and, owing to the gastrocolic or ileopyloric reflex, is likely to come on immediately after eating. Since the pain may occur in various segments of the colon, it is subject to considerable misinterpretation. When combined with tenderness of the left iliac fossa, it may suggest diverticulitis; of the epigastrium, peptic ulcer; of the right upper quadrant, gallbladder disease, and of the right lower quadrant, appendicitis. Appendectomy had been performed in 22 per cent of a series of 654 private "colitis" cases, or one and one-quarter times the general incidence (17 per cent in 3,000 unselected cases).[21] Feldman,[15] Jordan and Kiefer[19] and Eggleston[13] also reported a high incidence of appendectomy in cases of unstable colon. Furthermore, the incidence of colonic instability in my appendectomized patients was higher than in the general series, in the proportion of 49 per cent to 39 per cent. Finally, colonic pain may be referred to the left upper quadrant or even into the left side of the chest, when heart disease may be suggested.

Many patients with unstable colon suffer from so-called autointoxication. This has already been discussed briefly in the section on constipation. The occurrence of associated symptoms of neurogenic origin, varying from easy fatigability to headaches, nervousness and depression, has been appropriately stressed by Jordan.[3b]

It is sometimes stated that colonic instability is a forerunner of "idiopathic" ulcerative colitis. My experience fails to show any basis for this belief, and in my opinion, the two conditions are essentially different, even though at times they may be found together.

Diagnosis.—The history is usually characteristic. Physical examination may reveal tenderness over various parts of the colon, especially on the left side. Stool examination is important. The movements are unformed and often contain mucus. A sour odor is very suggestive. Proctoscopy reveals spasm, mucosal engorgement and mucous hypersecretion; it excludes ulcerative and proliferative organic lesions.

Roentgen examination shows alteration in both colon form and function. To be absolutely complete, this should include an opaque meal and an opaque enema. If only a single observation can be made, a film taken nine hours after the ingestion of a standard barium meal will be found to give maximum information. (This holds true only for the "prepared" barium meal as purchased. For the plain barium-water mixture, *e. g.*, 3 ounces of barium sulfate to 6 ounces of water, the interval probably should be reduced to between seven and eight hours.) This will reveal hypermotility by showing that the head of the barium column has reached the pelvic colon or rectum at that time, and it will also show characteristic changes in the colon form, such as irregularity or loss of haustra and streaking or "feathering" of the fecal column.[20] These characteristics are illustrated in figure 115.

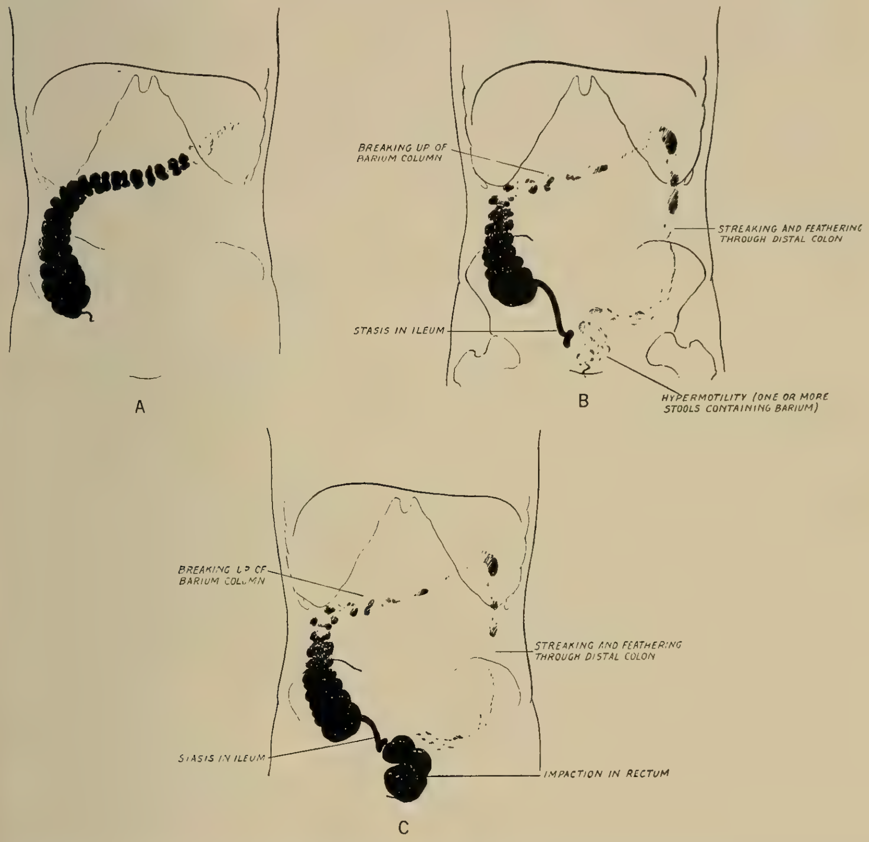
A
BREAKING UP OF BARIUM COLUMN
STREAKING AND FEATHERING THROUGH DISTAL COLON
STASIS IN ILEUM
HYPERMOTILITY (ONE OR MORE STOOLS CONTAINING BARIUM)
B
BREAKING UP OF BARIUM COLUMN
STREAKING AND FEATHERING THROUGH DISTAL COLON
STASIS IN ILEUM
IMPACTION IN RECTUM
C

FIG. 115.—Nine hour observations: *A*, normal colon; *B*, unstable colon, phase of diarrhea; *C*, unstable colon, phase of constipation. (Kantor, 1932, courtesy of *Southern Medical Journal*.)

The opaque enema gives equally valuable information. The amount required to fill the entire colon is reduced even below the average mentioned for the spastic colon in the constipated phase. One of my patients an adult, required but 10 ounces. The haustra are numerous and deep cutting and occasionally are the site of numerous superimposed small, shallow wavelets giving the bowel a striking serrated appearance, which Mills[33] called fibrillation. In some cases, on the other hand, the distal part of the colon appears smoother than normal. Here one approaches the borderline of the "tape" or "band" colon, an appearance usually considered characteristic of ulcerative colitis. In such cases great care must be exercised in the differential diagnosis.

Recently interest has been aroused over the possibility of studying the mucosal surface of the colon by a special enema technic based on the use of a thin layer of opaque material distributed over the bowel surface by gentle pressure.[5] According to Lust,[30] in simple chronic colitis the mucosa shows changes in both transverse and longitudinal rugae, and there is demonstrable a partial loss of colonic elasticity, whereby distention is still possible but the capacity for normal contraction is definitely impaired. Obviously, further studies by this method are desirable.

Differential Diagnosis.—In peptic ulcer the pain is localized above the navel, comes later after meals and is relieved by administration of food and alkalis; there may be bleeding or vomiting; the stools do not contain mucus, and the *x*-ray findings are characteristic. In gallbladder disease the pain is much more intense and may require opiates; the radiation is backward and upward to the shoulder; the attacks are discrete; there may be jaundice; the stools may be normal, and the *x*-ray findings are specific. Differentiation from colonic carcinoma and diverticulitis is clinched by proctoscopic and roentgen study. Cardiac disease is revealed by physical examination and electrocardiography, and appendicitis is diagnosed at the bedside.

Treatment.—The main effort should be directed toward restoration of the normal bowel function. This stabilization requires the skilful coördination of reassurance, relaxation and reëducation, the three "R's" of successful bowel management.

All forms of colonic abuse (cathartics, enemas, irrigation) should be completely withdrawn, and constipation should be treated as described in the previous section. Apprehension and insomnia should be overcome by appropriate psychotherapy and the judicious use of sedatives and somnifacients. The outdoor life, exercise such as golf or boating, change of scene and environment and various forms of hydrotherapy and physiotherapy are all useful. Exercise is contraindicated, however, if pain is prominent, when rest and belladonna (in ascending doses of the tincture) are usually effective.

The diet should be based on a bland regimen, such as the Schmidt plan of feeding,[25] but milk should be excluded as well as all cold fluids. Meat, fish, fowl and all high grade proteins which leave little residue are exceedingly well tolerated. Ripe bananas, though they contain considerable fiber, are often welcome additions to the basic diet. When actual food idiosyncrasies exist, appropriate restrictions should be followed,[38] but in such cases the nutrition should be maintained by increased intake of permitted foodstuffs and by the liberal use of butter, which is fortunately well tolerated. For all patients, exposure to cold and wet should be scrupulously avoided.

Inert bulky drugs, such as kaolin, barium sulfate and aluminum hydroxide, not only seem to furnish a framework for the feces in the absence of natural but irritating roughage but tend to absorb or precipitate bacteria and toxins. There are many such preparations on the market, but it should be noted that the ordinary barium powder mixture used for *x*-ray diagnosis is an excellent therapeutic preparation. The usual dose is 1 tablespoonful in water two or three times daily. More active "detoxification" can be secured with castor oil or with the more modern sodium ricinoleate.[8] Some workers[32] combine the sodium ricinoleate with increasing doses of *Bacillus coli* vaccine given by hypodermic injection.

For the treatment of the underlying nervous or psychic disturbance it is essential to understand the manner in which symptoms result from subconscious maladjustments and to apply this knowledge in the study of the personality pattern and life situation of each patient. In most cases no elaborate psychotherapeutic procedures are either practical or desirable. Since most neurotic persons are more or less apprehensive, the method and manner of the physician are important. A thorough physical and laboratory examination will answer many questions and pave the way for the elimination of symptoms. In addition, a careful explanation of the nature of a neurosis and its differentiation from organic disease will prove helpful to many patients. Others will be relieved if they find in their physician an experienced person who will listen to their troubles, an authority who will be able and willing to answer their questions and a guide who will change their distorted viewpoint to a more confident and orderly outlook on life.[25]

For those patients who are not relieved by such simple measures, special psychotherapeutic assistance must be invoked. Some of the technical procedures practiced by psychoanalysts involve the transference of pent-up emotions to the physician, the recall of childhood memories and, finally, the abreaction of emotions—*i. e.*, the discharge, through insight, of an emotional complex so that the need for the continuance of symptoms no longer exists.[45] Although the results of such management are often successful, psychoanalytic treatment is difficult and usually time consuming, and is not always applicable since in some cases the psychosis or neurosis seems to constitute the best available adjustment to an "insoluble" situation.

Mucous colitis is discussed in Sir Arthur Hurst's chapter.

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CHAPTER XXVII

PROTOZOAL INFECTIONS OF THE INTESTINE

INTRODUCTION

THE intestinal tract of man may be parasitized by several organisms belonging to the protozoa, that division of the animal kingdom containing only unicellar animals. The protozoan parasites of the human intestine belong to three of the four classes of the protozoa, that is, to the rhizopoda, the mastigophora and the ciliata. Of the rhizopoda, five distinct species belonging to the order Amoebidae parasitize man, *i. e.*, *Endamoeba histolytica, Endamoeba coli, Endolimax nana, Iodamoeba bütschlii* and *Dientamoeba fragilis.* Of the mastigophora, five species belonging to the order Protomonadida are involved, *i. e.*, *Embadomonas intestinalis, Chilomastix mesnili, Enteromonas hominis, Trichomonas hominis* and *Giardia lamblia.* Of the ciliata, two species of the order Heterotrichida are concerned, *i. e.*, *Nyctotherus faba* and *Balantidium coli.*

Only two of these organisms, *i. e.*, *Endamoeba histolytica* and *Balantidium coli,* produce lesions and symptoms of importance, the others being either nonpathogenic or of doubtful pathogenicity.

AMEBIASIS

Synonyms.—Amebic dysentery, amebic colitis, amebic enteritis, intestinal amebiasis, visceral amebiasis, entamebiasis and endamebiasis.

Definition.—The term "amebiasis" includes all clinical types of infection of man with the pathogenic ameba *E. histolytica,* including latent infection with this parasite. The old conception that amebic dysentery covered all the clinical types of infection with this parasite is no longer held valid, for it is recognized today that this ameba is the cause of a host of clinical symptoms distinct from those observed during an attack of amebic dysentery and that the later is only a symptom complex comparatively rarely observed in infections with *E. histolytica.*

Etiology.—*E. histolytica* has three stages in its life cycle, a motile, or *trophozoite*, stage; a *precystic* stage, and an immotile, or *cystic*, stage. The motile forms, or *trophozoites,* occur in semifluid or fluid stools, while the cystic forms usually occur in semiformed or formed stools. The precystic forms may occur in either formed or fluid stools and are simply rounded-up trophozoites prior to encystment. The structure of *E. histolytica* differs in its various stages of development and will be considered in the discussion of the diagnosis of infection with this parasite (*vide infra,* p. 584).

E. histolytica is the only pathogenic ameba living in the human intestine, its habitat being the lower portion of the ileum, the appendix and any portion of the large intestine. It usually is most common in the region of the ileocecal valve, the flexures of the large gut and the rectum. It is a true tissue parasite and probably cannot live for any great length of time in the lumen of the intestine without invading the tissues and producing lesions. Invasion of the wall of the intestine is accomplished partly through the progressive ameboid movements of the ameba and partly through secretion by the organism of cytolytic substances which soften and dissolve the tissues, thus enabling the ameba to penetrate them. The motile forms of the ameba, the trophozoites, penetrate the tissues and produce lesions, and cysts are not formed in the tissues of man but only in the bowel lumen when conditions become unfavorable for reproduction of the trophozoites.

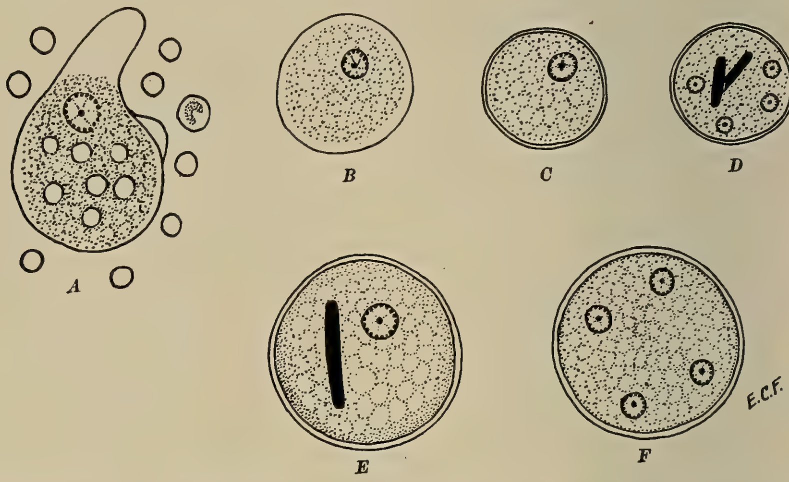

FIG. 116.—Life cycle and structure of *Endamoeba histolytica*: *A*, active trophozoite; *B*, precystic stage; *C* and *D*, small race of cysts; *E* and *F*, large race of cysts (*A* and *B*, × 1,100; *C* to *F*, × 1,360). (From Craig and Faust, *Clinical Parasitology*, after Faust in the *Journal of Laboratory and Clinical Medicine*.)

The *life cycle* of *E. histolytica* is simple. The cysts which have been voided in the feces of the infected person are swallowed in food or drink contaminated by such material and, passing through the stomach and small intestine, excyst in the lower portion of the ileum and in the ascending colon, each cyst liberating an ameba possessing four nuclei. After liberation from the cysts the four-nucleated ameba divides, according to some authorities into four and according to others into eight motile trophozoites. The trophozoites divide by simple binary fission both in the lumen of the gut and in the tissues and are the invading forms of the ameba, the cysts being the infective forms. Division in the tissues continues indefinitely, but in the lumen of the gut division is limited, and when conditions become unfavorable the trophozoites round up, secrete a cyst wall and become cysts. The rounded form are called precystic and are simply intermediate between the trophozoites and the cysts.

After encystment and while the cysts are still in the lumen of the intestine, division of the nucleus occurs until in the fully developed cyst four nuclei are produced, this number rarely being exceeded although cysts containing eight nuclei have been observed. The cysts are passed in the feces of the infected person and do not excyst unless they are swallowed in contaminated food or drink, when the cycle is repeated. If the cysts in the uninucleate condition are voided in the stools, division of the nucleus may occur without the body, according to Hegner, Johnson and Stabler (1932) and Tsuchiya (1932), and four-nucleated cysts may thus be produced. The cysts formed within the intestine of the host do not excyst in the host so far as is known.

The *etiologic relation* of *E. histolytica* to the lesions observed in amebiasis is undoubted at present, and the organism is recognized as the cause of the form of dysentery known as amebic dysentery and of many other clinical conditions comprised in the infection known as amebiasis. Early in the history of this parasite it was found to be associated with specific ulcerative lesions in man and in experimental animals—dogs, kittens and monkeys—as well as with the symptom complex recognized as amebic abscess of the liver. It remained for Walker and Sellards, in 1913, to demonstrate this relation beyond any doubt in experiments on man. Since their experiments it has been accepted as proved that *E. histolytica* is the cause of the lesions with which it is associated, and further work on experimental animals has furnished abundant confirmation of this thesis.

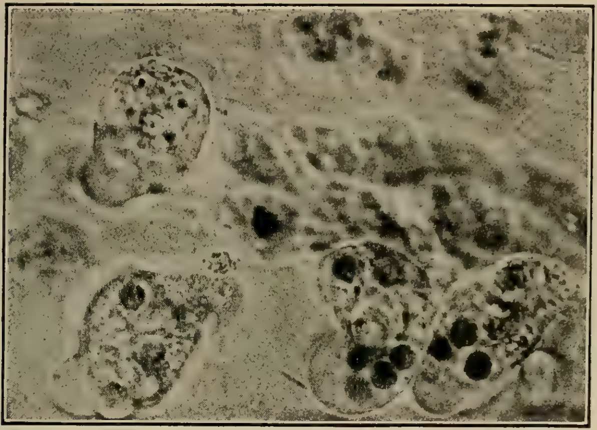

Fig. 117.—Unstained preparation of stool, showing *Endamoeba histolytica*. There are four motile trophozoites, the three in the lower part of the illustration containing red blood corpuscles (× 750). (From Craig and Faust, *Clinical Parasitology*, from a preparation by Craig in the Army Medical Museum Collection.)

Epidemiology.—The transmission of amebiasis depends on the ingestion of food or drink contaminated with material containing the cysts of *E. histolytica*, for while it has been proved by Craig (1905), Swartzwelder and others that the motile trophozoites may pass through the stomach of experimental animals such as kittens and dogs without injury and cause infection, the chances that food or drink may become contaminated by feces containing the motile forms are small, for the trophozoites perish so quickly in fecal material after it is passed that food or drink would have to be contaminated almost immediately with freshly passed material, which would certainly almost never occur.

The *resistance of the cysts* of *E. histolytica* to chemical and physical agents is important, as these are the infective forms of parasite. Drying kills the cysts almost immediately, but in fecal material kept in a cool, shaded and moist place the cysts may remain viable for from nine to twenty-one days, and if the weather is cool, as long as three months, while in the icebox at 32 F. Stone found that the cysts remained alive for as long as fourteen months. Water will keep the cysts viable for from one to five weeks, according to its richness in bacteria, the cysts dying more quickly in badly polluted than in pure water. The cysts will remain alive in a 1 : 2,500 solution of bichloride of mercury for thirty minutes, in 0.5 per cent solution of formalin for thirty minutes and in 2 per cent solution of potassium permanganate for three days. It is usually estimated that in order to kill the cysts in water, many times the amount of chlorine usually employed in water sterilization for bacteria is required. In the intestinal tract of flies and cockroaches the cysts of *E. histolytica* remain viable for some time, and their droppings have been found to contain viable cysts for as long as forty-eight hours after passage. Naturally infected flies have been found by several observers.

Infection of some of the lower animals, dogs, monkeys, rats and pigs, under natural conditions has been proved by several authorities. It is not known how important any of these animal reservoirs is in the transmission of amebiasis to man.

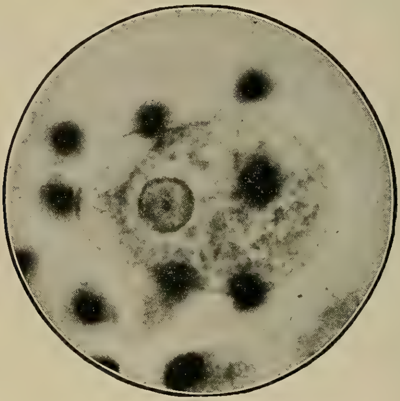

FIG. 118.—*Endamoeba histolytica:* Trophozoite stained with iron hematoxylin, showing the typical nuclear structure of the species. Note the delicate nuclear membrane lined with minute chromatin granules and the minute central karyosome (× 680). (From Craig and Faust, *Clinical Parasitology,* from a preparation by Craig in the Army Medical School Collection.)

The *incidence of infection* with *E. histolytica* varies greatly in different regions and is always higher in improperly sanitated localities and in the tropics and subtropics than in well sanitated districts and in the temperate zones. In 1926 I estimated, on the basis of my own and other authors' surveys, that approximately 10 per cent of the population of the United States was infected with this parasite. This was received with much skepticism at that time, but since then many surveys have been made, and the results have well justified my estimate. Most authorities believe that the total incidence of infection is even higher. This percentage does not hold true for all parts of this country but varies much in different localities. In other parts of the world the percentage of infection also varies greatly, and in some tropical regions from 40 to 60 per cent of the inhabitants harbor this parasite.

An epidemiologic problem of great importance is that of the possible *existence of strains of* E. histolytica *of low virulence* or of nonvirulent strains. In 1928, Brumpt described an ameba identical in structure with *E. histolytica,* which he called *Entamoeba dispar* and which was slightly pathogenic for kittens and did not produce any symptoms in man. His observations were confirmed by Simic (1921–1933) but have not been accepted by most authorities. I have never been able to confirm the existence of such an ameba and believe that Brumpt's *Entamoeba dispar* is simply a small race of *E. histolytica* of diminished virulence. However, I believe that not all strains of *E. histolytica* are equal in virulence, and the careful and extensive work of Meleney and Frye (1933–1937) in the production of amebiasis in kittens demonstrates that differences in virulence occur, persist and are important, in the epidemiology of the infection. On the other hand, I do not believe that any strain of this parasite has yet been found that is nonpathogenic to man, and Meleney and Frye were unable to find a nonpathogenic strain for kittens. Faust and Swartzwelder (1936) reported that the passage of a strain of *E. histolytica* through successive animals (dogs) resulted in a marked increase in the virulence of the strain, and this observation helps to explain the excessive virulence observed in epidemics of amebiasis, as in that originating in Chicago (*vide infra*).

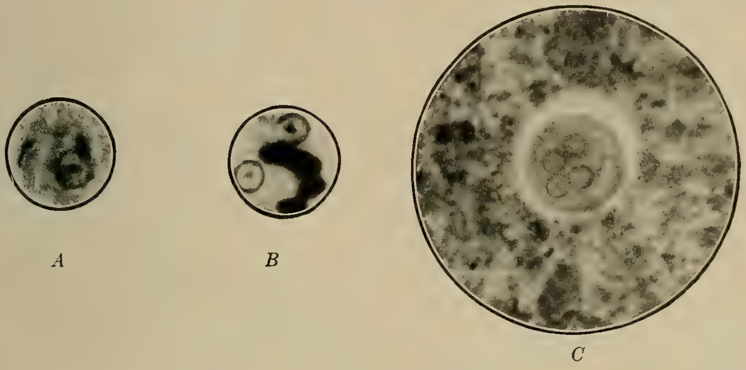

Fig. 119.—*Endamoeba histolytica*, stained with iron hematoxylin (× 750): *A*, cyst containing one nucleus and chromatoidal bodies; *B*, cyst containing two nuclei and a large chromatoidal mass; *C*, cyst containing four nuclei. (From Craig and Faust, *Clinical Parasitology*, from a preparation by Craig in the Army Medical Museum Collection.)

It has been suggested that the strains of this ameba observed in symptomless carriers are probably less virulent than those observed in persons presenting symptoms, but this has not been found true by animal experimentation. Likewise, in my laboratories and elsewhere lesions produced in dogs by the inoculation of small cysts have been just as severe as those following inoculation of large ones.

The usual *methods of transmission* of *E. histolytica* from person to person are through the contamination of food or drink by material containing the cysts of the parasite. Transmission may be accomplished through a contaminated water supply, through food or drink contaminated by an infected food handler, through the droppings of flies or other insects and through the employment of human excrement in the fertilization of vegetable gardens. Other routes of transmission are possible, for example, through the water of swimming pools, but those aforementioned are the most important.

Epidemics of Amebiasis.—Although typically endemic, under favorable conditions amebiasis and amebic dysentery may occur in epidemic form. (This has been denied by some protozoölogists with no practical experience in the field.) Limited epidemics of amebic dysentery were of frequent occurrence among American soldiers in the field during the Philippine insurrection and were mentioned by me many years ago (1905). In 1916 I observed an epidemic at El Paso, Texas, among the military personnel, during which, within three months, over 100 cases occurred. The most striking epidemic of amebic dysentery on record was that originating in a hotel in Chicago in 1933, during which 1,050 cases of amebic dysentery occurred, with 70 deaths. This epidemic was caused by the pollution of the stored water supplied the hotel by cross-connections with a sewer. Examples could be multiplied, but this is unnecessary.

General Factors.—Certain general factors may influence the occurrence of amebiasis, for instance, age, sex, race, food supply and climate.

Age.—Amebiasis is most often observed in early and middle adult life, which may be explained by the greater chances of exposure of the young and middle-aged adult and by the character of the food supply of infants and children, while in the aged a more or less active acquired immunity may be present owing to repeated natural infections.

Sex.—Males appear to be more frequently affected than females. This is probably due to greater exposure, for in some localities females have been found more frequently infected than males.

Race.—In natives of areas highly endemic for the infection apparently some immunity develops from repeated infection, but this immunity pertains only to the clinical effects. Thus, in such regions a high percentage of persons infected with *E. histolytica* present no clinical evidence of the infection, while in infected nonresidents severe symptoms usually occur.

Food Supply.—The incidence of symptomatic infections is higher in persons subsisting on an unsuitable or starvation diet than in others. A proper food supply undoubtedly increases the resistance to this infection. In addition, if the results of the experimental work of Hegner and of Faust, Scott and Swartzwelder (1936) on dogs can be interpreted as applicable to man, certain foods markedly influence the severity of an amebic infection.

Climate.—While the greater prevalence of amebiasis in the tropics and subtropics may be explained largely by the lack of sanitation in these regions, the much greater clinical severity of the infection certainly is due to the depressing effect of such climates on resistance to the infection. It has always been recognized that the removal of the patient suffering from amebic dysentery from a tropical to a cool climate is invariably followed by marked improvement in the clinical condition, even without treatment.

The subject of *immunity in amebiasis* is little understood. Where the disease is highly endemic, infection occurs in natives as in non-natives, but severe symptoms are much less common in the former group. That infection with *E. histolytica* leads to the production of certain so-called immune bodies was demonstrated by the work of Wagener (1924), who found precipitins in the blood serum of infected persons, and by my work (1927) and that of many others, who have demonstrated complement-fixing bodies in the blood serum of such persons.

Pathology.—The lesions vary with the degree of invasion of the tissues and with the location. They are primarily produced by hemolytic and cytolytic substances secreted by the ameba, which soften and dissolve the cells surrounding the invading parasite. In pure infections with the ameba there is no evidence of an inflammatory reaction on the part of the invaded tissue and no cellular infiltration, which is always present in bacterial invasion. However, secondary bacterial infection is almost invariably present, to some extent at least, in macroscopic lesions, and in these there is marked cellular infiltration. It is impossible to be sure just how much of the pathologic picture is due to the ameba and how much to the complicating bacterial infection. However, even in the mixed infections the pathologic picture of amebic invasion of the intestine and other tissues is characteristic.

Carriers and Persons With Mild Infections.—Some authorities apparently believe that in symptomless carriers or cyst passers definite lesions caused by this parasite do not occur. However, many investigators have demonstrated that even severe ulceration of the intestine may be present with this class of amebic infection. The pathology of amebiasis in carriers has been especially studied by Dock (1891), Musgrave (1910), Bartlett (1917) and Craig (1934); microscopic lesions of the intestinal wall existed in every carrier examined, and macroscopic ulceration was present in the majority. The term "healthy carrier" should not be used if by it is meant one in whom no lesions produced by this parasite are present. The recognition of this fact is most important from a clinical standpoint, as will be noted later.

In all carriers there exist *microscopic* lesions of the intestine varying in severity from minute areas of cytolysis and necrosis of the mucous membrane to typical ulcerations almost invisible to the naked eye. The *macroscopic* lesions observed in intestinal amebiasis in carriers consist of cytolyzed, slightly inflamed areas in the mucous membrane, pinpoint-sized depigmented areas representing the site of healed ulcers and small ulcers of typical structure. More rarely, large ulcers may be present with the characteristic structure of those observed in the intestine in amebic dysentery. The observation by Bartlett that when symptoms do occur in intestinal amebiasis marked ulceration is already present in the intestine is concurred in by me from my observations on the pathology of amebiasis in carriers.

The pathologic lesions observed in persons presenting atypical or mild symptoms of amebic infection are like those observed in symptomless carriers, but definite macroscopic ulceration is more frequently encountered.

Patients With Definite Intestinal Symptoms Without Dysentery.—As will be noted later, a large group of persons with infection with *E. histolytica* have definite intestinal symptoms but no dysentery. The lesions present in these persons are similar to those in carriers, but severe ulceration of the intestine is usually present and the lesions so closely resemble those present with amebic dysentery that they prove beyond question that marked ulceration may occur in the intestine without dysentery and that the latter symptom complex is by no means the typical one observed in amebiasis.

Patients With Amebic Dysentery.—The pathologic picture of amebic dysentery is characteristic, and as this symptom complex is simply the most severe stage of amebiasis, one finds all the lesions mentioned as occurring in carriers and in persons with mild and with severe infections not accompanied by dysentery. The lesions present are absolutely typical, even though a secondary bacterial infection is invariably present. Mixed infections of bacillary and amebic dysentery occur rarely and sometimes complicate the pathologic picture, but even in such infections the amebic nature of a portion of the picture is clearly discernible.

In the intestinal tract of patients dying of amebic dysentery all the characteristic lesions of intestinal amebiasis are present. The invasion of the mucous membrane results in the formation of pockets beneath the mucous membrane containing a glairy material consisting of mucus, cytolyzed and necrotic material and numerous amebas. These pockets communicate with the lumen of the gut through a pinhead-sized opening and generally project into the lumen, producing the appearance of small tubercles with a minute opening at the apex. Eventually these lesions break down, and ulcers with overhanging edges are produced, the floor being formed by the mucous, submucous or muscular coat of the intestine. Other ulcers have rounded edges, and many of these communicate with one another beneath or through the mucous membrane by means of channels containing material like that in the pockets produced by invasion of the mucous membrane by the amebas. Ulcers not infrequently merge into one another and thus produce large, irregular ulcerative areas, which may encircle the gut. In some instances the burrowing of the amebas beneath the mucous membrane and the resulting cytolysis and necrosis of the invaded tissues result in the separation of gangrenous sloughs and shreds of tissue, giving the interior of the intestine the "buffalo-skin" appearance mentioned by older writers on amebic dysentery. The ulcers may extend to the peritoneal coat and result in perforation of the intestine, while in rare instances granulomatous masses resembling papillomas may be produced, especially in the rectum, and may lead to a diagnosis of malignant change.

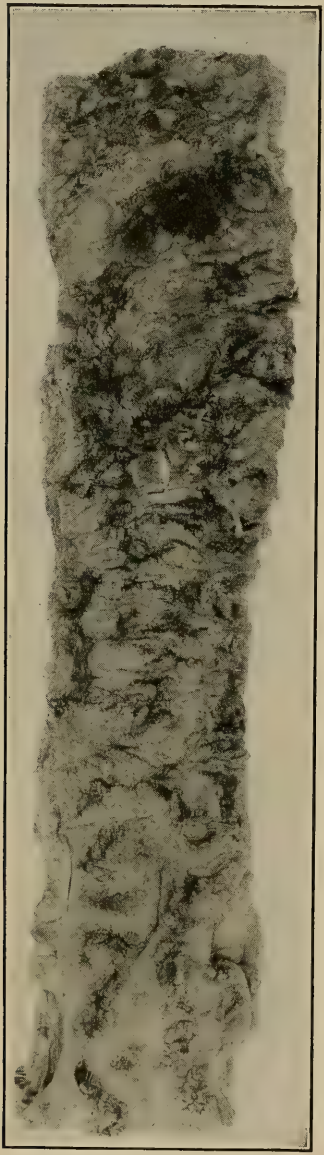

FIG. 120.—Section of colon, showing lesions of acute amebic dysentery Note the irregular shape of the ulcers, the overhanging ragged edges and the sinuses through the mucous membrane connecting some of the ulcers. (From Craig, *Amebiasis and Amebic Dysentery*; courtesy of Charles C Thomas. Photograph by the Army Medical Museum.)

In fulminant amebic infections, in which death may occur in a few days, the entire mucous and submucous coats of the intestine may present marked inflammatory changes, and large areas may be gangrenous. Ulcerations may be present if the infection has been chronic before the onset of the fulminant symptoms, but usually these are not marked and there are generalized inflammation and superficial necrosis. I believe that fulminant infections are invariably combined infections of amebas and bacteria, especially the dysentery bacilli or streptococci, *Invasion of the appendix* by *E. histolytica* is not infrequent, and the appendix may show no macroscopic evidence of the invasion or it may be inflamed and edematous, with ulcerations present in the mucous or submucous coat. In many cases a complicating bacterial infection will produce the pathologic picture usually observed in acute appendicitis, and the amebic element will not be recognized.

In *healing,* very small intestinal ulcerations leave a minute pigmented area, while larger ulcers heal with the formation of fibrous scar tissue. In long-standing intestinal amebias, the healing of the ulcers may result in such large collections of dense fibrous scar tissue that the intestine may be constricted in places, and the intestinal coats are always greatly thickened.

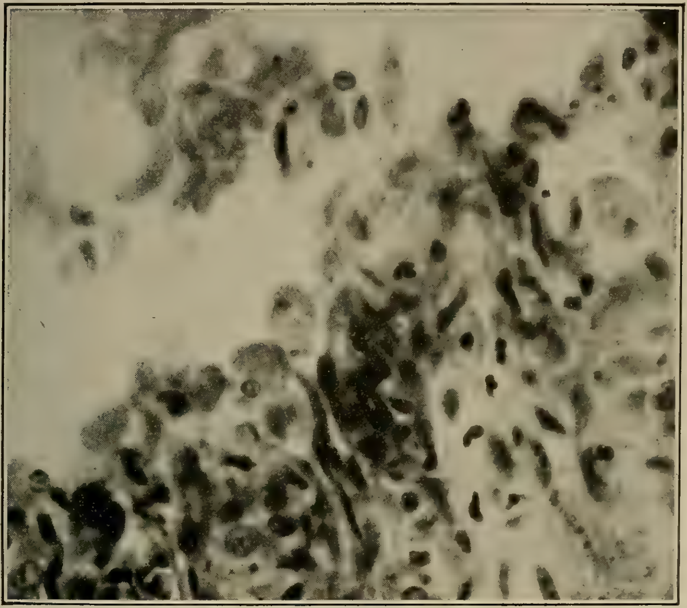

Fig. 121.—Section of intestine, showing *Endamoeba histolytica* just entering the mucous coat and some organisms within the glands, a condition present in carriers of the parasite without symptoms, representing the earliest stage of invasion of the tissues (× 380). (From Craig, *Amebiasis, and Amebic Dysentery*; courtesy of Charles C Thomas. From the collection of Drs. William M. James and Lawrence Getz, at the Army Medical Museum.)

The *microscopic pathology* of intestinal amebiasis is also characteristic, there being an absence of round cell infiltration around the lesions unless a secondary bacterial infection is present. The amebas are seen in the cytolyzed areas in the mucous, submucous or muscular coat of the intestine, either in groups or singly, within and around the glands and not infrequently within the capillaries and lymph spaces. Only trophozoites are found in the invaded tissues. These multiply by simple binary fission, producing nests of amebas, and from such nests the organisms invade the surrounding tissues. In carriers and in persons with mild infection only the mucous membrane may be attacked, but with more severe infection the amebas may be seen in all the intestinal coats, especially if the symptoms of amebic dysentery are present. In carriers and persons with mild infection healing of the minute lesions rapidly occurs, and there may be an invasion of the submucous or muscular coat without resulting ulceration, as shown by the presence of numerous amebas in these locations with no evidence of ulceration. This is important from the clinical standpoint, for most writers apparently believe that ulceration must invariably follow the invasion of the tissues of the intestine. These observations indicate that the amebas *per se* are not responsible for much of the ulceration present in severe infections, but that secondary bacterial infections are chiefly concerned.

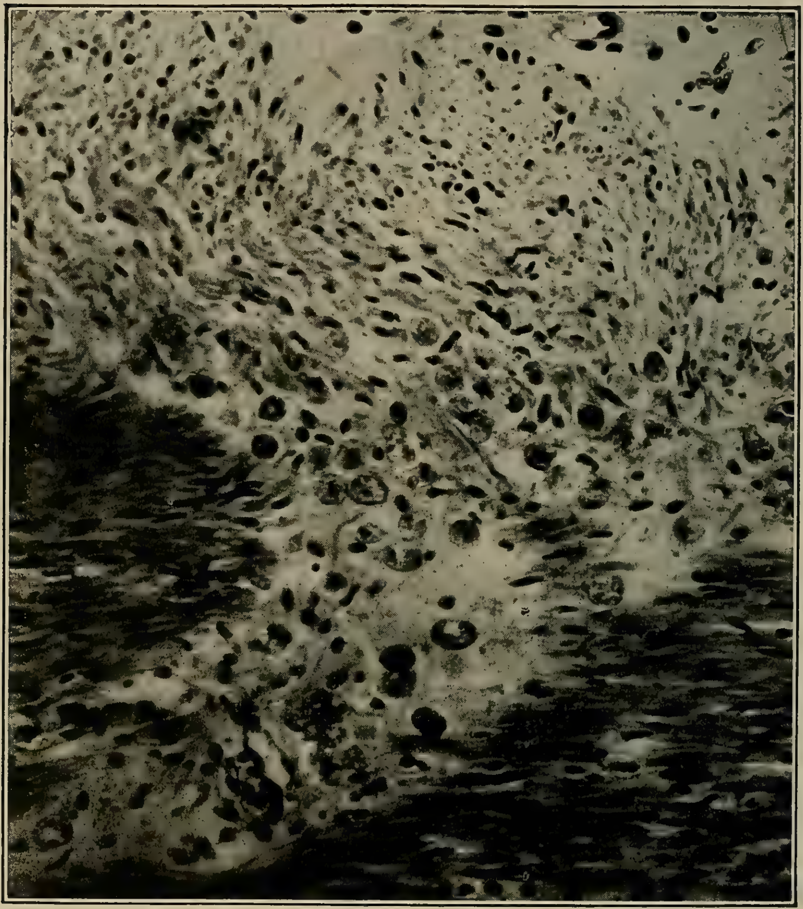

FIG. 122.—Section of the colon, showing invasion of the submucous and muscular coats of the intestine by *Endamoeba histolytica*. Note the extensive cytolysis of the submucosa and the border of the muscular coat and the large number of amebas present, as well as the absence of any acute inflammatory action (× 170). (From Craig, *Amebiasis and Amebic Dysentery*; courtesy of Charles C Thomas. From a preparation in the collection of Drs. William M. James and Lawrence Getz, at the Army Medical Museum.)

Symptomatology.—The symptoms of amebiasis are protean, as one would expect from the pathology. Clinically they vary in severity from slight gastrointestinal disturbances to those of a fulminating amebic dysentery or those inhibited in amebic hepatitis or in amebic abscess of the liver or of other organs. In severe infections the symptoms may be typical of acute amebic dysentery, while in the milder infections they may be so slight or atypical as to be unrecognized or neglected as of no importance.

Class 1, Symptomless Carriers or Cyst Passers.—It has been estimated that approximately 50 per cent of persons infected with *E. histolytica* do not at the time they are examined show any symptoms of the infection, although a careful inquiry into the medical history of many of them demonstrates that they have had symptoms that might have been caused by the parasite, and if reëxaminations over a period were possible many of them would show symptoms later. It should always be remembered that in all these persons the amebias are continually invading the mucous membrane of the intestine and that an amebic hepatitis or an amebic abscess of the liver may develop without appreciable intestinal symptoms ever having occurred. These persons possess great resistance to the infection, and the minute lesions made by the amebias in invading the tissues rapidly heal in most instances, although, as already shown, macroscopic ulceration of the intestine may occur.

Class 2, Carriers With Symptoms and Persons With Mild Symptomatic Infections.—Because careful inquiry of supposed symptomless carriers often results in the discovery of symptoms of the infection identical with those observed in persons with mild symptomatic infections, the two groups will be considered together. The symptoms present in such infections are confined almost entirely to the gastrointestinal tract and nervous system and are seldom recognized as being caused by this parasite unless one is experienced in the study of amebiasis. The symptoms are not pathognomonic, but their occurrence should always suggest the possible presence of *E. histolytica* and should lead to an examination of the stools.

Gastrointestinal symptoms are constipation alternating with normal bowel movements or slight evanescent attacks of diarrhea, colicky pains in the lower part of the abdomen, slight nausea before or after eating, a capricious appetite, anorexia, gaseous eructations after eating and gaseous distention of the abdomen and pain and tenderness in the right iliac fossa or over the ascending colon in the ileocecal region.

Nervous symptoms are a dull, more or less constant headache, usually frontal and especially marked in the early morning hours; aching in the muscles of the arms and legs or neuralgic pains in these muscles and in the lumbar muscles; sleepiness or disturbed slumber; depression of spirits, and a loss of mental alertness associated with a poor memory. A subnormal temperature is frequent, especially in the early morning, and the afternoon temperature seldom reaches normal.

Circulatory symptoms are an irritable, easily accelerated pulse; vasomotor disturbances, such as flushing of the skin and sweating, especially of the palms and the soles; arrhythmias; sensations of faintness, and tachycardia.

The physical signs are below normal weight, a very common and important sign, a sallow skin, a mild secondary anemia, tenderness on deep pressure over the ileocecal region or various parts of the colon, abdominal distention and, in the presence of mild amebic hepatitis, which frequently occurs, tenderness over the liver.

It should be remembered that not all these symptoms and physical signs are found in every case, and there may be any combination of them. The most common symptom is constipation, contrary to the usual belief that an infection with *E. histolytica* always causes diarrhea or dysentery. Slight diarrheal attacks lasting for a few hours may occur. Over-indulgence in sweet or fatty food or in alcoholic beverages is frequently followed by a diarrheal attack in otherwise symptomless carriers.

Most of the symptoms are those commonly observed with a low grade septic infection. The constant production of minute lesions in the mucous membrane of the intestine and the possibility of bacteria penetrating into the intestinal tissues through these lesions would lead one to expect this. Physicians do not hesitate to blame a small abscess at the root of a tooth for the symptoms characteristic of a focal infection, but one seldom hears anything said about focal infections in the intestine. The lesions of mild infections with *E. histolytica* are in reality potential sources of infection and undoubtedly as important in this respect as an abscessed tooth, owing to their number and the constant danger of the invasion of the walls of the intestine by pathogenic bacteria present in the lumen of the gut. I have previously stated (1934):

> The writer is convinced that a considerable proportion of the patients, who crowd our gastro-enterological clinics complaining of vague and indefinite symptoms connected with the gastro-intestinal tract, deriving no benefit from various methods of treatment, and in whom the gastro-enterologist is unable to arrive at a diagnosis, are really carriers of *Endamoeba histolytica*, and the symptoms present are caused by this parasite. The absence of a history of continuous diarrhea or dysentery in these carriers often leads to a neglect of a stool examination for the amebae, the diagnosis is thus missed, and the patient is treated for some other condition supposed to be present or he is regarded as a hypochondriac or neurasthenic.

Class 3, Patients Suffering From Severe Diarrheal Attacks.—Attacks of severe diarrhea occur at irregular intervals, last for varying periods and are followed usually by periods of constipation. The symptoms noted with mild infections are intensified, and the physical signs are more marked. The diarrheal attacks may occur after a dietary indiscretion or from over-indulgence in alcoholic beverages or without any appreciable stimulus. They may last for days, weeks or months and may (rarely) be accompanied by a slight fever. The stools are of a semifluid or fluid consistency and small in amount if numerous and may contain mucus but no blood. They are usually passed without tenesmus but are accompanied by colicky abdominal pains. Diarrheal attacks during the night or in the early morning are especially apt to occur in amebiasis, and the number of stools may vary from three or four to as many as ten or twelve during the twenty-four hours. Usually the attacks do not last for more than a week, but in some cases chronic diarrhea may persist for months, from three to six stools being passed daily. Between the attacks of diarrhea the patient is usually constipated but may have normal bowel movements. The stools contain numerous motile trophozoites of *E. histolytica* during the diarrheal attacks and cysts after the stools become formed. The term "amebic enteritis" is sometimes applied to diarrhea caused by this organism.

Class 4, Patients Suffering From Acute and Chronic Amebic Dysentery.—The term "amebic dysentery" has been used by the older medical writers, and, unfortunately, by some modern authors, to indicate a form of dysentery which they regarded, and do regard, as a disease *sui generis*. Today it is known that amebic dysentery is simply a symptom complex occurring during severe infections with *E. histolytica* as a late stage. In fact, it is difficult to draw the line between comparatively mild infections with this parasite, in which minute amounts of blood are present in the stools, and those in which larger amounts are passed and which are usually classed as amebic dysentery. If one includes all amebic infections in which the stools may contain macroscopic blood as amebic dysentery, one will include a large number of infections in which none of the other typical symptoms of the disease occur and which should not be dignified by that term. In this discussion of the subject I shall include only those infections in which several bloody and mucoid stools are passed daily, accompanied by other symptoms associated with the condition usually described as amebic dysentery.

In the older writings there is usually a discussion of the *period of incubation* of amebic dysentery, but it is rarely possible to be sure just when infections with *E. histolytica* occur, and hence it is impossible to determine the period of incubation. Dysenteric symptoms may occur a few days after infection, provided the infective dose of the cysts be large, as happened with some of the persons infected in the Chicago epidemic, or such symptoms may not be observed for months or years after infection.

The onset of the symptoms of amebic dysentery may be sudden or preceded by days or weeks of mild symptoms like those observed in class 2 or class 3 infection. If the onset is sudden, the symptoms consist of an attack of abdominal colic succeeded by the passage of semifluid or fluid stools, at first free from blood but soon becoming bloody and mucoid. There may be a chill or chilly sensations and a rise of a degree or two in the temperature, although fever is not usually present. The number of bowel movements gradually increases until the patient is passing as many as twenty or more a day. If the movements are numerous, the material passed consists almost entirely of mucus and blood, and tenesmus is marked, while if the attack is mild, tenesmus may be almost absent and the stools contain more fecal material and less mucus and blood. There are all degrees of severity in attacks of amebic dysentery, from the mildest ones with from six to eight bowel movements daily to fulminant infections in which thirty to forty stools may occur daily and death may follow in a few days. With these fulminant infections I believe there is always a complicating infection with strains of dysentery bacilli or streptococci.

Prostration is not severe at first, as a rule, but increases gradually in long-continued attacks. In fulminant infections prostration is marked from the beginning, and the symptoms are those of an overwhelming toxemia. Usually there are anorexia, gaseous eructations and distention of the abdomen, headache, insomnia, aching in the muscles of the back and legs, mental depression and a weak and irritable pulse. In very severe attacks all these symptoms are intensified, with marked weakness and prostration.

The stools during the dysenteric attack contain numerous motile trophozoites of *E. histolytica,* many of them containing red blood corpuscles, clumps of which, owing to agglutination, are frequently present in the dejecta. In uncomplicated infections few pus cells occur, but with secondary bacterial infection, pus cells are numerous.

The duration of an attack varies greatly, from three days to several weeks, without treatment. The fulminant attacks may result in death within a few days or be succeeded by a chronic dysentery, or recovery may occur after two or three weeks, even without treatment. The severity and duration apparently depend on the extent of the ulceration in the intestine, the resistance of the patient to the infection and the presence or absence of serious secondary bacterial infection.

The *symptoms of chronic amebic dysentery* are essentially those observed during acute amebic dysentery, with intervals in which no symptoms are present or in which chronic constipation is prominent. Chronic amebic dysentery is not a disease entity but simply a succession of attacks of acute amebic dysentery, each succeeded by an interval in which no symptoms may be present or the symptoms are those of a mild infection. In some cases, after the symptoms of the primary acute dysenteric attack have subsided, a period of more or less diarrhea may persist, while in others after the primary acute attack there may be severe constipation for some time. The patient during the intervals enjoys fairly good health. Such chronic infections may last for months or years, but the acute symptoms usually become less pronounced with succeeding dysenteric attacks, and spontaneous recovery may occur in some instances. In long-continued infections a chronic diarrhea may occur even after the amebic infection has disappeared, owing to the replacement of large amounts of mucous membrane by dense scar tissue, this hindering the absorption of fluid from the intestine. With chronic amebic dysentery amebic hepatitis or an amebic abscess of the liver frequently develops, the onset being accompanied by fever, pain, tenderness over the liver and a moderate leukocytosis. With chronic disease the complexion is sallow; there is always a secondary anemia, and usually there is more or less emaciation. Repeated dysenteric attacks lead to chronic invalidism, and the symptoms noted between the attacks are those of class 2 or 3 infection.

Complications.—Amebic abscess of the liver is frequent in the tropics and subtropics but comparatively rare in temperate climates. The percentage of infections complicated by abscess of the liver varies so much in different localities that it impossible to give a general average which would be of any scientific value.

Predisposing causes appear to be *sex* (males suffer from this complication much more frequently than females, the ratio being approximately 7 to 1); *age* (this complication occurs most frequently between the ages of twenty-one and forty and rarely in infants and young children); *exposure and starvation*, and *preceding attacks of amebic dysentery*. However, there is frequently no history of previous diarrhea or dysentery, and the complication may occur even in symptomless carriers. In 21 of 52 cases (over 40 per cent) of amebic liver abscess observed by Ochsner and DeBakey (1935) there was no history of a previous diarrhea or dysentery, and my experience has been similar.

An amebic abscess of the liver may also develop in persons who have recovered months or even years before, so that the absence of *E. histolytica* from the stools should not be considered as proof that such an abscess does not exist if suspicious symptoms are present. Of 131 cases of amebic liver abscess studied by Ochsner and DeBakey (1935), examination of the stools for this ameba gave negative results in no less than 65.9 per cent at the time of operation, while many other authorities have reported negative results in from 20 to as high as 65 per cent of such cases. An amebic abscess of the liver may develop during an attack of amebic dysentery, but this is not a frequent occurrence.

A common complication of amebic abscess of the liver is rupture, which may occur into the right pleural cavity, the right lung, the peritoneum, the pericardium, the colon, the kidney or the vena cava. The most common sites of rupture are the right pleural cavity and the right lung.

The *pathologic picture* of this condition is diagnostic. The organ is enlarged, and the abscesses may be single or multiple, the characteristic finding being a large single abscess at the dome in the right lobe. The abscesses vary greatly in size, the smaller and more recently developed ones consisting of grayish brown oval or rounded areas of cytolyzed and necrotic tissue without a definite abscess wall, while the larger and order ones have a definite wall of varying thickness enclosing partially liquefied material containing cytolyzed and necrotic liver cells, connective tissue fragments and red blood corpuscles. In many abscesses strands of the connective tissue framework of the organ may be seen stretching across the abscess cavity, this tissue being more resistant to the cytolytic action of the amebas than the parenchyma of the liver. Lying between these undestroyed fibers of connective tissue, the characteristic amebic liver abscess "pus" is seen, chocolate brown in uncomplicated infections and consisting of the elements aforementioned together with trophozoites of *E. histolytica*. This material is not pus, for pus cells are not present except in the presence of a secondary bacterial complication, when the contents of the abscess cavity may be yellow or green, multitudes of pus cells are present and the typical "anchovy sauce" appearance of the contents is lost. From 40 to 50 per cent of amebic abscesses of the liver are complicated by a secondary bacterial infection in my experience.

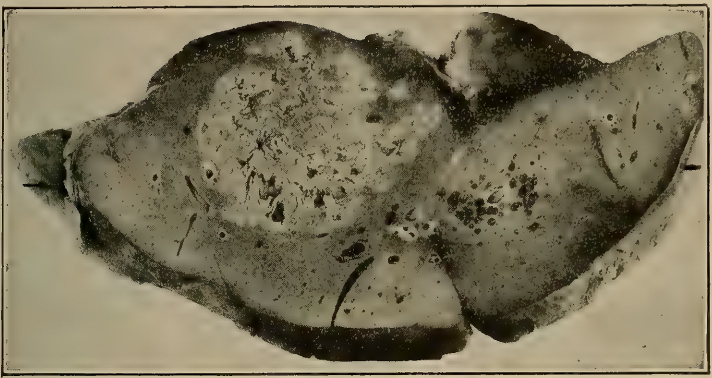

FIG. 123.—Large solitary amebic abscess of the liver. The cytolysis of the liver tissue is not complete, and there is no well defined abscess wall. (From Craig, *Amebiasis and Amebic Dysentery*; courtesy of Charles C Thomas. From the Army Medical School Collection.)

The trophozoites of *E. histolytica* are found in the abscess contents in the smaller and larger abscesses if a secondary bacterial infection is not present and are also observed in the tissue of the abscess wall externally, where they may be seen invading the surrounding tissues. In the old abscesses it is difficult to demonstrate the amebas either in the contents or in the wall of the abscess, and with the usual secondary bacterial infection they cannot be demonstrated in the contents. The amebas usually reach the liver through the portal circulation, but there is good evidence that sometimes they may reach the organ through the lymphatic vessels or even through the peritoneal cavity.

The *symptoms* of an amebic abscess of the liver are usually preceded by those of amebic hepatitis. This "presuppurative stage," described by Rogers (1935), is important, as it is amenable to treatment, and its recognition and proper treatment may prevent the development of an abscess. The liver is slightly enlarged and tender on deep pressure, and there is usually a sense of discomfort or aching. A daily remittent fever is present, and the leukocyte count varies between 15,000 and 30,000, the neutrophilic leukocytes being increased. Following these symptoms, those of an amebic abscess of the liver may supervene, or the hepatitis may become chronic or spontaneously disappear.

The symptoms of liver abscess are a remittent fever, occurring daily or for irregular periods; pain and tenderness over the liver, the pain being often referred to the right shoulder, the axilla or the back; sweating during the febrile remissions, which usually occur during the early morning hours, and leukocytosis, the total leukocyte count varying from 10,000 to 50,000 cells per cubic centimeter and the neutrophilic leukocytes being relatively increased. The physical signs are a sallow skin, jaundice, lusterless conjunctivas, below normal weight and marked emaciation when the condition is of long standing, a weak, irregular pulse and enlargement of the liver, most frequently upward, the dome of the liver bulging into the diaphragm. With amebic liver abscess of long standing the appearance is usually cachectic, much resembling that with malignant disease of the liver or intestine.

Fever, pain and tenderness over the liver and leukocytosis should always be regarded as suspicious of amebic hepatitis or amebic abscess of the liver in persons known to be infected with *E. histolytica* or who reside in regions having a high endemic index for this parasite. Even today the diagnosis of these conditions is frequently made only at the autopsy table or is entirely missed.

Amebic abscess of the lung, next in frequency, is usually secondary to an amebic abscess of the liver which has ruptured into the pleural cavity or into the base of the right lung through an adherent diaphragm. A primary amebic abscess of the lung is rare, and the symptoms are those of pulmonary tuberculosis—anorexia, nausea, fever, chills, sweating, pain over the lung, a chronic hacking cough and the expectoration of rusty sputum containing red blood corpuscles and motile trophozoites of *E. histolytica.* The physical signs are diminished breath sounds, coarse or bubbling rales, dulness over the affected region and a secondary anemia of moderate grade.

With amebic abscess of the lung following the rupture of an amebic abscess of the liver, the symptoms are similar to those of primary lung abscess. They may occur suddenly, as severe pain in the lung at the time of the rupture of the liver abscess, but usually they develop gradually after the rupture. Empyema is frequently present, and pleurisy often occurs. Fever, chills and sweating, always present, taken together with the cough, expectoration and physical signs, frequently lead to a diagnosis of pulmonary tuberculosis. I have observed several cases in which a large amebic abscess was found in the lung and the liver at autopsy after a diagnosis of death from chronic pulmonary tuberculosis. There are usually a moderate leukocytosis (between 16,000 and 25,000 leukocytes per cubic millimeter) and a mild secondary anemia.

Abscess of the lung is usually single, although if secondary infection is present, numerous metastatic abscesses may occur. The abscess cavity usually connects wish a bronchus, and the patient coughs up the characteristic anchovy sauce-like material found in the abscess cavity. As in amebic abscess of the liver, the contents of the cavity consist of cytolyzed and necrotic tissue cells, red blood corpuscles and trophozoites of *E. histolytica*, as well as Charcot-Leyden crystals, but with secondary bacterial infection, which is very common, the contents of the abscess cavity consist largely of yellowish or greenish pus.

Other important complications of amebiasis are amebic appendicitis, abscess of the brain or other organs, amebiasis of the skin, invasion of the urinary bladder and the gallbladder, severe intestinal hemorrhage, perforation of an amebic ulcer of the intestine and peritonitis. All these, with the exception of amebic appendicitis, are rare complications, and the symptoms are those usually attending such complications of other conditions.

Amebic appendicitis is caused by the invasion of the tissues of the appendix of *E. histolytica* and may be acute or chronic. In the acute type the symptoms are those usually observed in appendicitis due to bacteria, and probably in all cases there is a secondary bacterial infection. In the much more common, chronic type the symptoms are similar to those of chronic bacterial appendicitis, there being recurrent attacks of more or less severe pain in the right iliac fossa and over the region of the appendix, slight fever and a leukocytosis during the febrile periods, a constant sense of discomfort in the right iliac fossa and constipation. The symptoms recur at irregular intervals and vary in duration, but are often indistinguishable from those of chronic appendicitis of bacterial origin. Since the development of my complement fixation test for the diagnosis of amebiasis, I have observed many persons with a diagnosis of chronic appendicitis who have a positive reaction to this test and whose stools were later found to contain *E. histolytica.* Many of these persons had been operated on for appendicitis prior to the examination for intestinal amebiasis, and sections of the appendix have shown the amebas within the tissues of the organ. Symptoms simulating those of acute or chronic appendicitis are frequently present with intestinal amebiasis even though the appendix is not involved, and patients with such symptoms have been operated on for a supposed attack, sometimes with fatal results. I should urge that, if possible, a careful examination of the stool be made for *E. histolytica* in every instance of symptoms of appendicitis before an operation is decided on, as such operations in cases of intestinal amebiasis are often attended with very serious results. A majority of the deaths occurring during the Chicago epidemic of amebiasis were in patients operated on for supposed appendicitis.

Sequelae.—In long-continued amebiasis certain sequelae of importance have been noted. The extensive destruction of the coats of the intestine through ulceration and necrosis when followed by healing of the lesions results in the formation of dense fibrous scar tissue, which may involve so much of the bowel that constrictions and even obstruction occur. The entire gut in places may be so thickened and contracted as to limit the size of the lumen, thus causing loss of function and in some cases obstinate constipation. Again the replacement of much of the absorptive surface of the intestine by dense fibrous scar tissue leads to nonabsorption of fluid from the gut and to chronic diarrhea, which the patient usually believes to be due to an existing amebic infection when such an infection may have been eliminated long since.

In many patients suffering from chronic amebic dysentery a condition develops which is frequently mistaken for sprue. The stools are copious, semifluid and gaseous and light yellow or almost white. The tongue becomes sore and appears red and swollen, and a secondary anemia is present. Mistakes in diagnosis are extremely frequent, especially in temperate regions where amebiasis is not believed to be present. The history of a preceding severe diarrhea or dysentery should serve to differetiate the condition from sprue in most cases.

Diagnosis.—The diagnosis of amebiasis must rest on the demonstration of *E. histolytica* in the stools or tissues, for even with apparently typical clinical amebic dysentery one cannot be sure of the diagnosis unless the causative parasite is demonstrated. The methods available for identification of the ameba are the microscopic examination of unstained and stained smears of the patient's feces, the cultivation of the ameba from the feces, the examination of sections of the affected tissues and the complement fixation test. The last is difficult from a technical standpoint and is not essential except in the rare instances of infection of the liver or other organs when the primary intestinal infection has disappeared. The use of the proctoscope in diagnosis is justifiable only when stool examinations show no amebas, and is useless in a large proportion of cases because rectal ulceration may not be present. The examination of scrapings obtained through the proctoscope from lesions due to *E. histolytica* should show the presence of motile trophozoites, but rarely does a proctoscopic examination demonstrate the amebas if repeated stool examinations, properly made, have failed to do so.

It is essential that *E. histolytica* be differentiated from the four other species of ameba living in the human intestine, all of which are harmless commensals, so far as is known. For this reason the diagnosis of amebiasis is frequently neglected or missed, although routine examinations of stools should be just as much a part of a physical examination as the examination of the urine or the blood.

These amebas are differentiated by their distinctive structure, and Table 21 gives their most important differential features. The reader is referred to my *Amebiasis and Amebic Dysentery* and to current works on parasitology for a detailed discussion of the structure of these organisms. If proper methods of examination be employed it is possible easily to differentiate *E. histolytica* from the other intestinal amebas by morphologic characteristics if one has been trained in such differentiation and has had practical experience in stool examinations. The motile trophozoites occur only in semifluid or fluid stools, and if the patient is passing formed stools, it will be necessary to administer a saline cathartic if one desires to obtain the motile amebas. On the other hand, the cysts of this parasite occur only in semiformed or formed stools, and it is practically useless to search for them in fluid stools.*

The *clinical diagnosis* of amebiasis is most difficult and is usually impossible unless the causative ameba can be demonstrated. Clinically, the various phases of amebiasis are often mistaken for other infections or diseases. *Bacillary dysentery* is differentiated by the greater prostration, the almost constant presence of fever, the arthritic symptoms and its usually epidemic occurrence. Its onset is also much more sudden as a rule than that of amebic dysentery. *Mucous colitis* can usually be differentiated by the occurrence of the characteristic mucous shreds and casts, as well as by the history. *Chronic ulceraıive colitis* can be differentiated in most instances by the more general distribution of the ulcerative lesions in the lower bowel, and it is here that the proctoscope is most valuable, although many amebic ulcerations resemble those found in ulcerative colitis and the differential diagnosis must depend on the presence or absence of *E. histolytica.* Ulcerative colitis may be complicates by an amebic infection, and *vice versa*. *Schistosomal* and *balantidial dysentaries* can be differentiated from amebic dysentery only by the demonstration of the respective causative organisms.

The diagnosis of *amebic abscess of the liver* is often difficult, but daily fever, leukocytosis and pain or tenderness over the hepatic region with enlargement of the liver are most suggestive symptoms of either an amebic hepatitis or an amebic abscess of the liver in one who has an intestinal amebiasis or a history of such infection. The diagnosis of *amebic abscess of the lung* must depend on the demonstration of *E. histolytica* in the sputum unless there is a clear history of a ruptured liver abscess into the lung, as the symptoms and physical signs closely mimic those of pulmonary tuberculosis, bronchiectasis and other diseases of the lung. The diagnosis of amebic abscess of other organs, of cutaneous amebiasis and of amebiasis of the urinary bladder and gallbladder depend on the demonstration of the ameba.

The Cellular Exudate in the Stool as an Aid in Diagnosis.—The differentiation of the various forms of bacillary dysentery and of inflammatory conditions in the large intestine causing diarrhea or dysentery from amebic dysentery may often be made by attention to the character of the cellular

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* The methods of preparing unstained and stained smears of feces for examination are given in works on laboratory diagnosis and parasitology, but for the demonstration of the motile forms all that is necessary is to place a minute amount of the material to be examined, preferably a little bloody mucus, if present, on a microscopic slide, cover it with a coverglass and examine with the high power ($\frac{1}{6}$ inch) dry objective, being careful to make the examinations in a well heated room, as cold quickly renders the amebas motionless. If in such a preparation an ameba is observed which possesses active progressive motility and contains red blood corpuscles, one is justified in making a diagnosis of infection by *E. histolytica*, as the other amebas occurring in the human intestine rarely if ever ingest red blood corpuscles. The same type of examination is useful in demonstrating the cysts of this ameba, the formed fecal material being emulsified in a little saline solution and a minute portion of this being placed on a microscopic slide and examined as already described. It is necessary in differentiating the cysts to add a drop or two of a strong iodine solution (Lugol's solution) to the emulsified material, as this stains the nuclei of the cysts and enables one to count them. The cysts of *E. histolytica* when fully developed contain four nuclei.

Cultivation is sometimes employed in diagnosis, and this ameba may be cultivated indefinitely on several mediums of simple composition. The reader is referred to my *Amebiasis and Amebic Dysentery* for a detailed discussion of the various methods of cultivation as well as the technic and results of the complement fixation test I devised, which is specific for infection with *E. histolytica*.

TABLE 21.—THE DIFFERENTIAL DIAGNOSTIC FEATURES OF THE INTESTINAL AMEBAS OF MAN
(From Craig and Faust: *Clinical Parasitology*)

	Endamoeba histolytica	*Endamoeba coli*	*Endolimax nana*	*Iodamoeba bütschlii*	*Dientamoeba fragilis*
"Vegetative" or Trophozoite Stage. Unstained					
Size in microns	15 to 60μ	15 to 50μ	6 to 15μ	8 to 20μ	5 to 12μ
Motility	Active; progressive and directional	Sluggish; rarely progressive and directional	Sluggishly progressive	Sluggishly progressive	Active and progressive
Pseudopodia	Finger shaped; hyaline and glass like; rapidly extruded	Shorter and more blunt; more granular; slowly extruded	Blunt and hyaline; very rapidly extruded	Blunt and hyaline; slowly extruded	Blunt and leaf like; hyaline
Inclusions	Red blood corpuscles; no bacteria in fresh specimens	Bacteria and other material; no blood corpuscles	Bacteria; no blood corpuscles	Bacteria; no blood corpuscles	Bacteria; no blood corpuscles
Nucleus	Invisible usually	Visible	Visible	Invisible	Invisible
"Vegetative" or Trophozoite Stage. Iron Hematoxylin Stain					
Nuclear membrane	Delicate; inner surface has single layer of minute chromatin dots	Thicker; inner surface lined with coarse chromatin dots	Intermediate in thickness; chromatin seldom present on inner surface	Thick; chromatin dots may be present on inner surface	Very delicate; no chromatin dots on inner surface
Karyosome	Minute and in center of nucleus	Much larger and eccentrically situated	Large and may be in center or to one side of center of nucleus	Large and granular, in center of nucleus	Large and composed of definite chromatin granules lying in a dimly stained matrix
Intranuclear chromatin	No chromatin between karyosome and nuclear membrane	Chromatin grains between karyosome and nuclear membrane	No chromatin between karyosome and nuclear membrane	....	No chromatin between karyosome and nuclear membrane
Inclusions	Red blood corpuscles; no bacteria unless degenerated	No red blood corpuscles; many bacteria and other material	No red blood corpuscles; many bacteria	No red blood corpuscles; bacteria	No red blood corpuscles; bacteria

		Cystic Stage.	*Iodine Smear Preparations*		
Size in microns	6 to 20μ	10 to 33μ	5 to 14μ	5 to 20μ	No cysts have been demonstrated
Shape	Usually spherical	Usually spherical	Spherical, ovoidal or ellipsoidal	Irregular	
Cytoplasm	Bright greenish yellow	Yellowish brown	Pale green with numerous refractile vacuoles	Yellowish green	
Glycogen mass	Diffuse and reddish brown	Dark brown and indefinite central mass with indistinct border	Usually absent, brownish and either diffuse or defined	Usually present, dark brown and sharply outlined	
Nuclei	1 to 4; minute central karyosome very refractive; nuclear membrane beaded and refractive	1 to 8 or more; nuclear membrane refractive and granular; karyosome eccentric	1 to 4; indistinct	Indistinct; one usually present	
		Cystic Stage.	*Iron Hematoxylin Stain*		
Size in microns	6 to 20μ	10 to 33μ	5 to 14μ	5 to 20μ	No cysts have been found
Shape	Usually spherical	Spherical	Oval or ellipsoidal	Irregular	
Cytoplasm	Alveolar, often vacuolated	Granular and vacuolated	Vacuolated with chromatin granules	Vacuolated; large glycogen vacuole usually present	
Chromatoidal bodies	Bar, oval or thick rodlike masses with rounded ends	Filamentous, thread like or splinter like with square or pointed ends	Small, spherical or bacilliform, often in a vacuole	Usually absent; when present small round or granular	
Nuclei	1 to 4; delicate membrane lined with minute chromatin granules; karyosome minute central dot	1 to 8 or more; thick nuclear membrane lined with large dots of chromatin or irregular masses; karyosome eccentrically placed and large	1 to 4; nuclear membrane indistinct; karyosome in a single or divided mass on or near nuclear membrane	1, rarely 2; nuclear membrane very thin, often indistinct; karyosome placed laterally and surrounded by large granules	

exudate present in the patient's stools. Willmore and Shearman (1916) were the first to call attention to this simple means of differentiation, and their observations have been confirmed and extended. In 1925, Callender wrote as follows:

> With only a microscope and slides, a relatively inexperienced man can make a presumptive diagnosis (of bacillary dysentery) which will be correct in 90 per cent of the cases without the use of stained preparations, a much higher percentage of positive results than one can ever hope to obtain by bacteriological methods, to say nothing of the delay and uncertainty involved in arriving at a bacterological diagnosis.

I am in accord with this statement of Callender and believe that a study of the cellular exudate in diarrheal and dysenteric conditions furnishes the general practitioner a simple and generally accurate method of differentiating amebic from other diarrheal or dysenteric conditions met in practice.

In bacillary dysenteries and in all diarrheal conditions caused by pyogenic bacterial infections of the large intestine the stools contain innumerable pus cells, while in uncomplicated amebic dysentery the stools are almost devoid of these cells. In bacillary dysenteries the nuclei of most of the pus cells show a toxic degeneration, while in amebic dysentery the few leukocytes present show evidences of destruction of the cytoplasm, the nuclei being surrounded by little or none. The name *pyknotic bodies* has been given to these cells, and they are very characteristic of amebic dysentery. In the stools of amebic dysentery Charcot-Leyden crystals frequently occur, while they are absent from the stools of bacillary or other forms of diarrhea or dysentery. In the stools of bacillary dysentery there occur large mononuclear cells, or macrophages, many of which contain red blood corpuscles and resemble the trophozoites of *E. histolytica*, for which they are frequently mistaken. However, if one remembers that these macrophage cells are never actively motile, such a mistake may be avoided, for the trophozoites of *E. histolytica* possess active, progressive, ameboid motility. In the stools of bacillary and other bacterial dysenteries the red blood corpuscles present are more or less evenly distributed throughout the microscopic field, whereas in those of amebic dysentery they are in irregular clumps caused by agglutination. The "ghost cells" of Callender are also present in bacillary dysentery stools and absent in the stools of amebic dysentery.

Prognosis.—The prognosis of amebiasis varies with the duration and severity of the infection. For carriers without symptoms and patients with mild symptoms it is excellent with proper treatment, but even for these the possibility of the development of an amebic abscess of the liver or other organ renders the prognosis uncertain unless the infection is promptly eliminated. For patients who have suffered one or two attacks of amebic dysentery the prognosis is also excellent with proper treatment, but for patients who have suffered frequent dysenteric attacks it becomes uncertain and is always grave, as death may follow from exhaustion, or an amebic abscess of the liver may develop. For the fulminant types of amebic dysentery, fortunately rare, the prognosis is very grave, and few patients recover even with the best of treatment. For amebic abscess of the liver the outlook is always grave, although with prompt diagnosis and treatment it is usually good. If the preceding amebic hepatitis is diagnosed and properly treated the prognosis is excellent, as in most cases cure can be accomplished before a liver abscess develops. For amebic abscess of the lung it is always grave, but many patients recover under treatment. For abscess of the brain it is hopeless, and this is also true for abscess of other organs that cannot be reached by operative procedures when the diagnosis is delayed. For amebic appendicitis it is good if the condition is promptly diagnosed and properly treated. Otherwise it is bad, as operation for this condition in the presence of severe intestinal amebiasis often has a fatal result.

Treatment.—Several drugs are specific in action and if properly employed will eliminate infections with *E. histolytica* in the vast majority of instances. The most useful of these drugs are chiniofon, diodoquin, vioform, carbarsone and emetine hydrochloride.

Treatment of Carriers and Persons With Mild Amebic Infections.—It is obvious that for these persons drugs should be employed, if possible, that will not interfere with the daily occupation. Such drugs are chiniofon, diodoquin, vioform and carbarsone. *Chiniofon,* originally introduced for the treatment of amebiasis by the Germans under the name of "Yatren" and marketed in this country under the name "anayodin" as well, is a synthetic preparation (iodoxyquinolinsulfonic acid) containing about 28 per cent iodine, on which it depends for its amebicidal properties. It is marketed in pills, each containing 0.25 Gm. (4 grains), and the dose for an adult is three or four pills three times a day for eight days. *Diodoquin* (5,7-diodo-8-hydroxyquinoline) contains 63.9 per cent iodine and is dispensed in tablets, each containing 0.21 Gm. (3.2 grains). The dose varies with the severity of symptoms, for "symptomless carriers" being from two to three tablets three times a day. For persons with symptoms, ten to twelve tablets per day should be administered. The drug is nontoxic, so far as reports have shown. Treatment should be continued for twenty days for all types of infection. *Vioform* (iodochlorhydroxyquinoline) contains from 38 to over 40 per cent iodine and is administered in capsules each containing 0.25 Gm. (4 grains). The dose for an adult is one pill three times a day for ten days, repeated after an interval of ten days without treatment. *Carbarsone* (4-carbaminophenylarsonic acid) contains 28 per cent arsenic. It is administered in capsules each containing 0.25 Gm. (4 grains), and the dose for an adult is one capsule morning and evening after meals, for ten days.

If *E. histolytica* is still present in the stools after the completion of treatment with any of these drugs, the course of treatment may be repeated after a week or ten days. I prefer chiniofon to vioform or carbarsone and as a routine use it as outlined, then make a careful examination of the stools for the parasite. If amebas are still present, I repeat the treatment after one week or substitute carbarsone or diodoquin. In administering carbarsone it should be borne in mind that it is an arsenical and should not be given to persons suffering from disease of the liver or kidneys, and symptoms of arsenical intolerance should be guarded against. Carbarsone, although the safest of all arsenical recommended in the treatment of amebiasis, has produced serious toxic symptoms in rare instances of idiosyncrasy to arsenic.

After treatment has been completed, an examination of the stools for *E. histolytica* should be made once a month for at least three months and the treatment repeated if trophozoites or cysts are found in the stools.

With the drugs mentioned it has been possible to eliminate the infection in at least 85 to 90 per cent of my cases in this class after one course of treatment and in practically all after repeated courses.

Treatment of Patients With Severe Diarrhea.—The treatment of class 3 infections differs from that of classes 1 and 2 if the patient is seen during a diarrheal attack, when confinement to bed should be enforced and the diarrhea controlled by the administration of emetine hydrochloride, one of the alkaloids of ipecacuanha. This drug, still regarded by some as specific in the treatment of amebic diarrhea and dysentery, is remarkably successful in controlling the acute diarrheal or dysenteric symptoms but is not capable of eliminating amebic infection in the majority of cases and is not as good an amebicidal drug as those previously mentioned. The true field of emetine is in the control of the symptoms mentioned, after which it should be discontinued and one of the other, more specific drugs substituted in treatment.

Emetine hydrochloride is administered preferably by subcutaneous injection, and the dose for an adult is 0.065 Gm. (1 grain) once a day for not to exceed twelve days. For severe involvement, this dose may be administered in the morning, and in the evening 0.03 Gm. ($\frac{1}{2}$ grain) may be given by mouth, but usually the oral administration of the additional amount is not necessary.

It should always be remembered that the drug is toxic and that when given in too large a dose or over too long a period it may cause severe diarrhea, myocarditis, neuritis, nervous prostration and great muscular weakness, and death may suddenly occur from cardiac failure. If toxic symptoms develop during treatment, the drug should be discontinued at once, and one of the other amebicidal drugs mentioned should be substituted if the patient's condition permits. Throughout the administration of emetine the patient should be confined to bed.

The treatment I should recommend is the administration of 0.065 Gm. (1 grain) of emetine hydrochloride subcutaneously (*never intravenously*) once a day until the diarrhea ceases, which with even the most severe disease occurs within ten days. If the diarrhea should persist after the drug has been administered for twelve days, this medication should be discontinued, as it is dangerous to administer for a longer time and some other cause is probably responsible for the diarrheal symptoms. After the diarrhea has been controlled with emetine, chiniofon or one of the other drugs already mentioned should be administered in the dose recommended. In my experience chiniofon or carbarsone gives the best results after emetine therapy, and chiniofon is to be preferred because it is less irritating to the intestine than carbarsone. Diodoquin is also useful in the follow-up treatment after the administration of emetine hydrochloride.

After treatment has been completed, the stools should be examined for *E. histolytica* once a month for at least three months, and if the parasite is found, treatment with either chiniofon, carbarsone or vioform should be repeated.

I desire to warn against the promiscuous administration of emetine, which is prevalent because of the belief that it is the most efficient known specific in the treatment of amebiasis. The drug is dangerous to employ for long periods, as it often is, and I have observed many instances of chronic poisoning with emetine and several instances of death following its improper administration. Emetine should be used only in the dose mentioned for the control of severe diarrhea and dysentery and should never be continued for more than twelve days. This drug should not be employed in the treatment of carriers or persons with mild infections with *E. histolytica.*

Treatment of Patients With Amebic Dysentery.—The treatment of acute amebic dysentery is identical with that of severe amebic diarrhea, just described. Much better results are obtained when the patient is at rest throughout the course of treatment than when he is allowed to be about, even though the dysenteric symptoms are not severe. Usually eight to ten injections of emetine hydrochloride will stop the dysenteric symptoms, but for old chronic infections emetine or any other drug may not prove effective. Some authorities recommend employing a daily enema of 200 cubic centimeters of a 2 per cent warm watery solution of chiniofon, the solution to be retained for several hours if possible. If chiniofon is administered in this manner it should also be given by mouth, 0.5 Gm. (7½ grains) three times a day, and the combined treatment should be continued for ten days. In my experience the use of enemas of chiniofon has not been attended with any greater success than the oral administration of the drug alone.

The treatment of chronic amebic dysentery during acute exacerbations is that of acute amebic dysentery, while during the intervals between acute attacks the patient should be treated with courses of chiniofon, diodoquin or carbarsone if the amebas still persist in the stools. The prospect of eliminating long-continued chronic amebic dysentery is poor, and the greater the number of acute exacerbations, the less the chance of successful therapy.

Treatment of Patients With Complications of Amebiasis.—The work of Leonard Rogers in demonstrating the great value of injections of emetine hydrochloride in the treatment of amebic hepatitis and of amebic abscess of the liver placed in the hands of the practitioner of medicine an almost specific remedy for amebic hepatitis and for early amebic liver abscess. As soon as amebic hepatitis is diagnosed, emetine hydrochloride should be administered subcutaneously, in a dose of 0.065 Gm. (1 grain) once a day for twelve consecutive days. This treatment almost invariably results in the disappearance of the symptoms of this condition and the elimination of the infection. The same treatment is often successful for early amebic abscess of the liver, and numerous authorities have reported the absorption and healing of amebic abscesses of considerable size after treatment with emetine hydrochloride. Even for conditions demanding operative treatment it is best to give a course of injections of emetine hydrochloride, as it has been found that convalescence and healing after operation are much more rapid when this drug has been administered. The operative treatment of amebic abscess of the liver is discussed in texts on surgery.

The treatment of other complications of amebiasis—amebic abscess of the lung, cutaneous amebiasis, hemorrhage, peritonitis, intestinal obstruction and amebic abscess of other organs—consists of appropriate surgical measures except in the case of amebic abscess of the lung and cutaneous amebiasis, for which the subcutaneous injection of emetine hydrochloride, as for amebic hepatitis, is recommended.

General Treatment.—Patients suffering from acute diarrhea or dysentery should be confined to bed. Diet is most important and during the diarrhea or dysentery should be liquid, consisting of broths, egg albumin and milk with lime water. As the stools become semisolid, pure or malted milk should be given with eggs, soft puddings and gruels. A full diet is gradually adopted during convalescence, care being taken to avoid all foods that are known to irritate the large intestine. Alcohol in any form should be forbidden, and this rule should be enforced for carriers and persons with mild infection as well as those with severe disease. There is no more potent cause of acute diarrheal or dysenteric symptoms in any infection with *E. histolytica* than indulgence in alcoholic beverages, and such symptoms frequently follow the ingestion of several alcoholic drinks during dinners or other celebrations. Tonics are usually indicated if the patient has suffered from attacks of severe diarrhea or dysentery, and a carefully regulated life is essential whenever it has been found impossible to eliminate the amebic infection. A change of climate from a warm to a cool, bracing one is most beneficial and sometimes is practically curative.

Other Drugs Employed in the Treatment of Amebiasis.—A host of drugs other than those mentioned have been employed in the treatment of amebiasis and, while most of them are more or less amebicidal in their action, none of them is more efficient than chiniofon, diodoquin, vioform, carbarsone or emetine hydrochloride. Among the most useful may be mentioned emetine bismuth iodide, acetarsone, treparsol and chaparro amargoso.

Prophylaxis.—The prevention of infections with *E. histolytica* depends on the prevention of contamination of food or drink by material containing the cysts of the parasite. This may be accomplished by the proper disposal of fecal material, the guarding of the water supply from fecal pollution, the examination of food handlers and their proper treatment if found infected and the protection of food and drink from flies, cockroaches and other insects that are potential transmitters of the parasite.

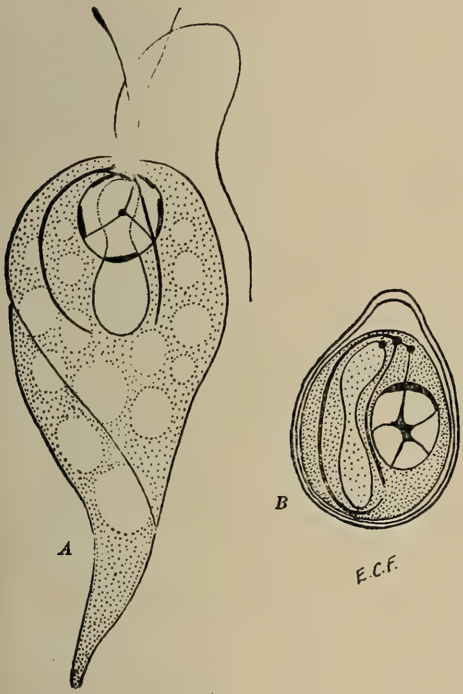
Other methods of prevention of value are instructing the public regarding the importance to public health of amebiasis and the steps in personal hygiene useful in its prevention; training laboratory personnel in stool examinations and differentiation of the various species of ameba living in the human intestine, and making amebiasis a reportable infection, so that proper measures may be taken by public health departments. In regions where the water supply is not impounded and filtered and amebiasis is endemic, the only method of rendering water safe is boiling, while in regions where human excrement is used for fertilizing gardens, as in the orient, one should abstain from eating uncooked fruits and vegetables.

Medicinal Prophylaxis.—In 1940 I recommended the use of diodoquin in the prevention of infection with *E. histolytica* for travelers in regions where the infection is endemic or for those who need not remain in such regions for long periods. The dose of diodoquin for this purpose should consist of seven tablets of 0.21 Gm. (3.2 grains) daily, two after breakfast and luncheon and three after dinner, and be continued for twenty days, if necessary. In many regions, where the infection is not prevalent, smaller prophylactic doses will probably be found effective.

INTESTINAL FLAGELLATE INFECTIONS

Of the five different species of protozoa belonging to the class Flagellata inhabiting the human intestine, only three occur frequently enough to be confused with more important parasites living in the intestine of man. These are *Chilomastix mesnili, Trichomonas hominis* and *Giardia lamblia.* They are all actively motile, motility depending on long whiplike flagella, assisted in *T. hominis* by an undulating membrane. Reproduction in all is by binary longitudinal fission during the motile, or trophozoite, stage, while in *C. mesnili* and *G. lamblia* cysts are formed when conditions are unfavorable for reproduction during the motile stage.

The **geographic distribution** of these flagellates is worldwide, but infections are much more common in the tropics and subtropics than in temperate regions, where it has been estimated that from 1 to 5 per cent of persons harbor one or more, *G. lamblia* being the most common, *C. mesnili* next and *T. hominis* least.



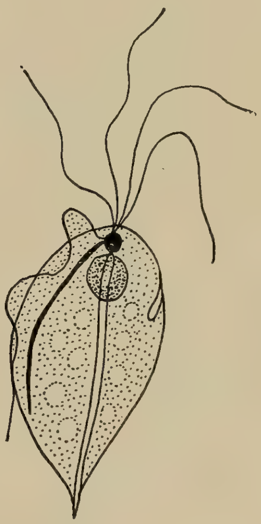


Fig. 124

Fig. 125

Fig. 124.—*Chilomastix mesnili: A*, trophozoite; *B*, cyst (× 3,200). The delicate flagellum within the cystostome is not shown. (From Craig and Faust, *Clinical Parasitology*, after Faust in the *Journal of Laboratory and Clinical Medicine.*)

Fig. 125.—*Trichomonas hominis* (× 1,600). (From Craig and Faust, *Clinical Parasitology*, after Faust in the *Journal of Laboratory and Clinical Medicine.*)

Their **relation to disease** is still undetermined. If they are present in large numbers, as they frequently are, it is conceivable that by their active movements they may increase and prolong an inflammatory condition in the intestine caused by some other factor, but while clinicians may believe that they are pathogenic because they are often associated with symptoms of diarrhea or dysentery, invariably a careful examination by qualified observers has demonstrated that the symptoms present were due to some other cause.

Of the three flagellates mentioned, *G. lamblia* has been reported most often as being associated with symptoms of disease, and a special form of dysentery known as "giardial" has been described by some writers as caused by this parasite. However, proper examinations were not made for the possible presence of one of the bacilli of bacillary dysentery or for *E. histolytica.* Since all the intestinal flagellates occur in any number in the motile stage only in semifluid or fluid stools, they are found most frequently when diarrhea or dysentery is present from any cause, and unless bacteriologic and protozoölogic examinations are made to eliminate other infections, the etiologic relation of any flagellate that may be present cannot be determined. Until it can be demonstrated that these flagellates produce definite lesions in the intestine of man they cannot be accepted as pathogenic.

Transmission is through the contamination of food or drink by material containing the cysts in the case of *C. mesnili* and of *G. lamblia* and the motile trophozoites in the case of *T. hominis.* Contamination may occur through infected food handlers, human excrement used for the fertilization of truck gardens, the droppings of flies and other insects and a water supply polluted by the improper disposal of sewage.

The **diagnosis** rests on demonstration of the parasites in the stools of the infected person, as in amebiasis. The motile forms are found in semifluid and fluid stools, while the cysts are found in semiformed or formed stools. All these flagellates are roughly pear shaped and hyaline and all have an active jerky motility in fluid stools. *G. lamblia* has eight flagella, two nuclei and a sucking disk which enables it to attach itself to the mucous membrane of the intestine. The cysts are oval and contain from two to four nuclei. The habitat of this flagellate is the small intestine, especially the duodenum. The motile form of *C. mesnili* has a large cleft at the anterior end called the cytostome, in which there is a short flagellum, and three anterior flagella, while the cysts are lemon shaped and contain a single nucleus. *T. hominis* has from four to five anterior flagella, an undulating membrane extending the entire length of the body and ending in a free posterior flagellum and a rigid structure called the axostyle extending through the body. No cysts have been demonstrated in the life cycle of this flagellate.

The **treatment** of infections with the intestinal flagellates, with the exception of *G. lamblia,* is not very satisfactory, for the reason that no specific drugs are known. The specific drugs for infections with *E. histolytica,* chiniofon, vioform, diodoquin and carbarsone, are only occasionally curative, and emetine hydrochloride is useless. In the treatment of infections with *G. lamblia* numerous clinicians have found atabrine specific, administered as in the treatment of a malaria infection, *i. e.,* 0.1 Gm. ($1\frac{1}{2}$ grains) three times daily for from three to five days. A reduced dose, 0.05 Gm. ($\frac{3}{4}$ grain), twice daily for not more than three days may be used for small children. Over 90 per cent of infections so treated have been eliminated.

Another compound that has been found still more efficient by some authorities is acranil, which is administered to adults in doses of 0.5 Gm. ($7\frac{1}{2}$ grains) three times a day for four or five days and to children of less than two years, one-half the adult dose, once a day for the same period. This compound is said to be nontoxic.

For the treatment of infections with *C. mesnili* and *T. hominis*, chiniofon, diodoquin and carbarsone are all sometimes successfully used as for infection with *E. histolytica,* but are not specific here.

Other drugs that have proved useful in some cases are acetarsone (stovarsol) and treparsol. These are not recommended, as they are more toxic than carbarsone and no more efficient. Methylene blue, dihydranol, carbon tetrachloride, the arsphenamines, bismuth subnitrate orally and various drugs injected *per rectum,* especially the silver salts, have sometimes eliminated infections with each of these flagellates but have much more often failed. Rectal injections cannot be expected to be of much value, as the flagellates live or are most numerous in the small intestine.

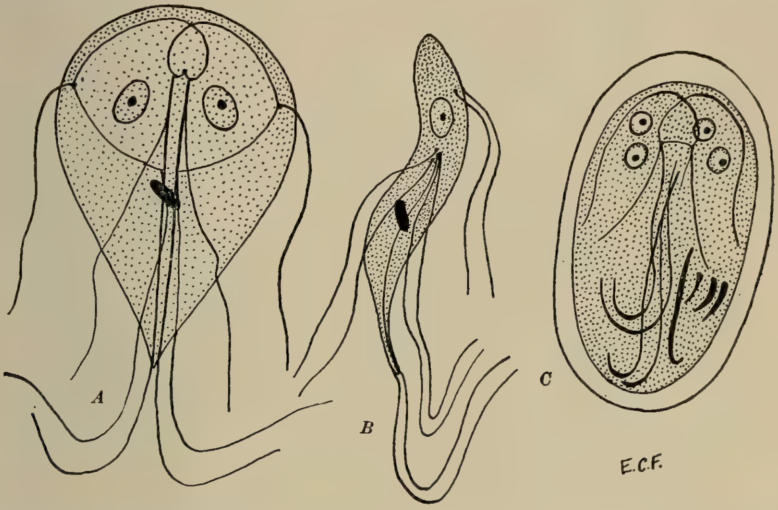


FIG. 126.—*Giardia lamblia: A,* ventral view of trophozoite; *B,* lateral view of trophozoite; *C,* cyst (× 4,800). (From Craig and Faust, *Clinical Parasitology,* after Faust in the *Journal of Laboratory and Clinical Medicine.*)

The **prevention of infection** consists in the prevention of the contamination of food or drink with fecal material containing the cysts of *G. lamblia* and *C. mesnili* and the trophozoites of *T. hominis.* The methods practiced for the prevention of infection with *E. histolytica* (*vide supra,* p. 592) are equally efficient here. As infections with the intestinal flagellates are not accompanied by lesions, their prevention is chiefly important because they are frequently complicated by infection with *E. histolytica.*

BALANTIDIASIS

Definition.—"Balantidiasis" may be defined as the infection of man with a protozoan organism belonging to the Ciliata, known as *Balantidium coli.* While this parasite primarily infects pigs, man is occasionally infected, with the production of ulcerative lesions in the intestine followed by symptoms of diarrhea or dysentery.

Geographic Distribution.—This parasite probably occurs wherever its natural host, the pig, is found.

Etiology.—*Bal. coli* is the largest of the protozoa infecting man. The trophozoites measure from 50 to 100 by 40 to 70 microns, while the cysts measure from 50 to 80 by 40 to 60 microns. The motile forms are ovoid, are covered externally by short, delicate fibrils called cilia and have a marked cleft at the anterior end called the mouth, or cytostome. Two contractile vacuoles are present in the cytoplasm, and there is a large nucleus, called the macronucleus, in contact with which is a minute nuclear body known as the micronucleus. The cysts are ovoid and usually contain a single balantidium, but sometimes conjugating forms are encysted and two balantidia are found within a cyst. Reproduction in the motile, or trophozoite, stage of development occurs by binary transverse division, and no reproduction occurs within the cysts, encystment being purely protective.

The *life history* is similar to that of *E. histolytica*. The trophozoites live in the large intestine and multiply in the lumen of the gut and in the tissues, which they penetrate by their active motility and perhaps by the aid of a cytolytic ferment which they may excrete. Reproduction of the motile forms by transverse division occurs as long as conditions are favorable; then the tropozoites become motionless and secrete a cyst wall, eventually becoming cysts. The cysts are the infective stage of the parasite, and when swallowed by man pass through the stomach and small intestine and excyst in the ileocecal region and the ascending colon, each cyst liberating a single balantidium unless conjugating organisms have become encysted, when two balantidia may be liberated. The liberated balantidia penetrate the walls of the intestine or again become encysted, and the life cycle is repeated. The motile forms are found in semifluid and fluid stools, while the cysts are found in semiformed or formed stools.

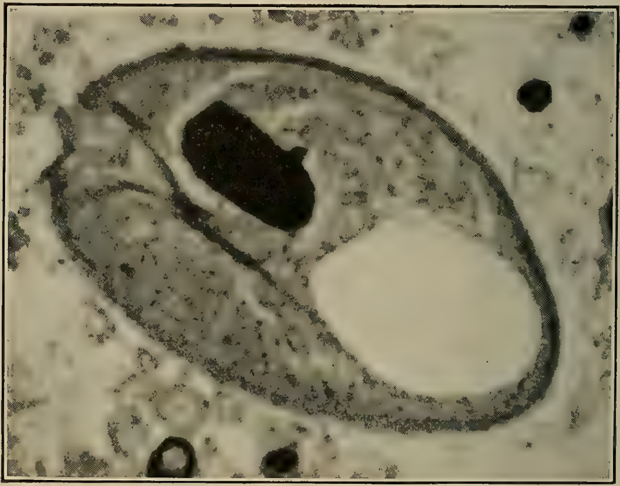


Fig. 127.—*Balantidium coli*, trophozoite in feces. (From Craig and Faust, *Clinical Parasitology*, from a preparation from the collection of Drs. William M. James and Lawrence Getz, at the Army Medical Museum.)

The *cultivation* of *Bal. coli* has been accomplished by many investigators, employing mediums that have been found efficient in the cultivation of *E. histolytica*.

The *relation of* Bal. coli *to disease* is unquestioned, but the organism may occur in the intestine of man without apparently producing lesions or symptoms. It is associated in man with characteristic ulcerative lesions in the large bowel and with symptoms of diarrhea and dysentery.

Epidemiology.—In the natural host, the pig, lesions are seldom found. The organism has been found also in naturally infected monkeys and orang-utans by Brook (1902–1903), and in rats by Awakian (1937). The infection of man follows the ingestion of food or drink contaminated by the feces of infected pigs or by human feces containing the cysts. Infection may also occur by direct transfer of pig feces to the mouth by the soiled hands of butchers or pig handlers. The cysts are very resistant to external influences and may remain alive in moist feces for as long as two months, while even in dry feces they have been found alive after two weeks. Ohi (1924) found that the cysts would resist a 1 : 1,000 solution of bichloride of mercury for one hour and a 5 per cent carbolic acid solution for six hours. Direct sunlight kills the cysts within three hours, according to Ohi.

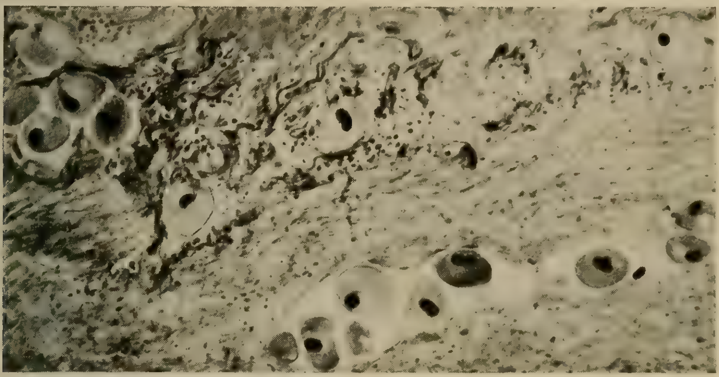


Fig. 128.—*Balantidium coli* in the submucous and muscular coats of the intestine. Areas of cytolysis are present around most of the balantidia. (From Tice, *Practice of Medicine*, from the Army Medical Museum.)

The *incidence of infection* with *Bal. coli* in man is small, although the parasite is very common in the pig. Faust and I, in the examination of the stools of many thousand persons in the Philippines, China and this country, observed but three dozen infections, and this small incidence has been noted by all investigators. Man is very resistant to infection with this parasite, although many infections are undoubtedly overlooked owing to the absence of symptoms.

Carriers of Bal. coli are sometimes sources of infection through the handling of food or drink, and infections may occur through a polluted water supply and the employment of pig feces in the fertilization of garden produce. Raisers of pigs and butchers are especially liable to infection, as already mentioned, by direct transfer of the feces of infected pigs to the mouth by the hands.

Pathology.—In many infections, especially in pigs, *Bal. coli* may live in the lumen of the large intestine for long periods without producing lesions but in man lesions are usually produced by the invasion of the coats of the intestine by the parasite. The lesions are ulcerative and macroscopically very similar to those produced by *E. histolytica*; abscesses form beneath the mucous membrane, and ulcers of various sizes may involve any or all the coats of the intestine. Microscopically, nests of balantidia may be observed within the mucous, submucous or muscular coat of the intestine, and unless there is a secondary bacterial infection present, the tissue surrounding these nests shows an area of cytolysis with no small round cell infiltration. The parasites are sometimes observed within the capillaries, and while they must occasionally reach the liver through the portal circulation, abscesses do not result as in infection with *E. histolytica.* The ulcers are sometimes connected by sinuses beneath and through the mucous membrane as in amebic dysentery, and the entire pathologic picture, both macroscopic and microscopic, is similar to that of the latter infection.

Symptomatology.—While *Bal. coli* may occur in the human intestine without producing definite symptoms, usually symptoms are present. These may be mild, consisting of gaseous eructations, discomfort after eating, anorexia, nausea, a capricious appetite, slight diarrhea and colicky pains in the abdomen; or severe, the aforementioned symptoms being accentuated and accompanied by marked diarrhea or dysentery. If dysentery is present, the symptoms are like those observed in amebic dysentery, and intervals of constipation may alternate with the diarrheal or dysenteric attacks, the clinical picture being that of an amebic enteritis or dysentery. Combined infections with *E. histolytica* or one of the dysentery baccili may occur.

Diagnosis.—The diagnosis of balantidiasis must rest on the demonstration of *Bal. coli* in the stools or tissues of the intestine. During life the diagnosis is easily made by placing a little of a semifluid or fluid stool on a microscopic slide, covering it with a coverglass and examining it with the high power dry objective. The large size and great activity of this organism render it easy of recognition. The cysts are also easily recognized, but are found only in semiformed or formed stools.

Prognosis.—The prognosis of balantidiasis is usually good; many patients recover without treatment, while for others various forms of treatment have been curative. However, fatal infections not infrequently occur, and the mortality rate has been placed by different authorities between 5 and 30 per cent. In my opinion the higher mortality rates reported have been due to the nonrecognition of the milder infections. In over forty years I have never observed a fatal infection with *Bal. coli,* but my experience may have been unusual. If marked dysenteric symptoms are present, the prognosis is grave; Fairley (1936) stated that such infections have shown a mortality rate of 29 per cent in his experience.

Treatment.—The elimination of this parasite has been apparently accomplished by several drugs. Walker (1913) obtained successful results in some cases with rectal injections of the organic silver preparations, while enemas of protargol have been recommended by several observers. The exact effect of the various specific amebicidal compounds, chiniofon, vioform, carbarsone and diodoquin, has not been determined, but these compounds merit a thorough trial for balantidiasis. Atabrine may be found useful. High colonic injections of solutions containing silver nitrate, quinine or iodine have been used with seeming success; other drugs recommended for treatment from time to time have been methylene blue, dihydranol, thymol, oil of chenopodium and santonin. Emetine is apparently useless for this infection.

It is apparent from the number of remedies that have been employed that none is recognized as specific, and the fact that so many infections disappear spontaneously renders it difficult to judge the efficiency of any remedy.

Prophylaxis.—The prophylaxis of balantidiasis consists in the prevention of the contamination of food or drink with fecal material containing the cysts of *Bal. coli.* So far as human infections are concerned, the methods employed in the prevention of amebiasis are efficient. As the pig is the natural host of *Bal. coli,* the feces of this animal should not be employed in fertilization, and all persons having to do with this animal should thoroughly cleanse their hands before eating or handling food. If the water supply is obtained from a local source, such as wells, springs or small streams, care should be taken that pigs are not allowed nearby.

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CHAPTER XXVIII

THE METAZOAN PARASITES OF THE GASTROINTESTINAL TRACT

INTRODUCTION

Metazoan parasites include all species of animals, other than the Protozoa, which have developed a parasitic mode of life. Tens of thousands have been described, and several hundred are known to parasitize man, although less than a score are sufficiently common or produce sufficiently severe symptoms to justify their consideration as important human parasites.

All the Metazoa which parasitize man belong to three large groups of the animal kingdom, the *Nemathelminthes* (roundworms and their allies), the *Platyhelminthes* (flatworms, including the tapeworms and the flukes) and the *Arthropoda* (comprehending the insects and their allies). Among the roundworm and flatworm parasites, all species which infect man are endoparasitic within the body, and the majority either live as adults in the intestinal tract or gain entrance to the body by being ingested and swallowed. On the other hand, except for accidental and temporary residence in the bowel, the Arthropoda are more directly related to the skin and the other somatic layers of the body. Nevertheless, many Arthropoda are of interest to the physician, because they serve as transmitters of pathogenic microörganisms to man.

Although the gastroenterologist is not primarily concerned with such diseases as malaria, yellow fever, dengue, filariasis, trypanosomiasis, kala-azar, rickettsia infections, relapsing fever and plague, all of which are usually acquired from the "bite" of some blood-sucking arthropod, the dysenteries, typhoid and cholera definitely concern him. These, in either endemic or epidemic form, are not infrequently transmitted to man through the intermediary of filth flies contaminating human food and drink.[9]

THE ROUNDWORMS (NEMATHELMINTHES)

These worms are more or less cylindrical and have a complete digestive tract. They vary from large worms like *Ascaris lumbricoides* to forms which are not visible to the naked eye. With few exceptions males and females are differentiated by external characters. The worms produce large numbers of eggs, which usually become embryonated and may hatch after they are expelled from the body. Ingestion of the fully embryonated egg (*Ascaris, Trichocephalus, Enterobius*), ingestion of a mature larva encysted in animal flesh (*Trichinella*) and invasion by the mature larva through the skin (hookworms, *Strongyloides,* filaria worms) constitute the characteristic ways by which roundworms gain entrance to the human body.[6]

Ascaris lumbricoides (The Giant Intestinal Roundworm), Producing Ascariasis. — Etiology and Biology. — These creamy, pinkish worms are about the size of a lead pencil, although they may be considerably smaller when present in large numbers. They have three distinct, fleshy lips at the oral end. The male is slightly smaller than the female and is somewhat curved at the caudal tip. Their normal habitat is the lumen of the small bowel. Here the females each lay 100,000 to 200,000 eggs daily. The fertile eggs (Fig. 138, 1) are broadly ovoid, measure 45 to 75 microns in length by 35 to 50 microns in transverse diameter, have a thick, grayish hyaline inner shell and a mammillated albuminoid outer shell, which is usually bile stained. They have a single heavily granular, spherical egg cell within the inner shell. Infertile eggs (Fig. 138, 2), which are frequently laid by these worms, are longer and narrower than fertile ones, are less regular in contour and have a disorganized mass of granules or globules within the inner shell.

When passed in feces the fertile eggs are unsegmented. They are very resistant to unfavorable conditions and require two or more weeks on the ground before they become embryonated. They are only then infective for man. On being picked up on soiled fingers or deposited on food and then swallowed, these eggs hatch in the small bowel, and the escaping larvae migrate into the intestinal wall and *via* the mesenteric lymphatic vessels or portal blood stream through the right chambers of the heart to the lungs. Here the larvae escape into the air sacs, migrate up the respiratory tree over the epiglottis and are swallowed. The incubation period is sixty to seventy-five days.[6]

Epidemiology.—Man acquires his infection from ingesting fully embryonated eggs which had previously been contaminated by human feces containing the unembryonated eggs. Small children are most commonly infected, owing to their habits of playing in the soil and then putting their fingers in their mouths. Small children are also primarily responsible for "seeding" the ground with eggs, as a result of their promiscuous defecations around the dooryard and even in the house. Once a soil has been "seeded" with eggs and these have become fully developed, the ground may remain infectious for many months. While ascariasis is most prevalent in warm climates, it is by no means rare in temperate zones. In American children it constitutes an important infection in the red clay areas of the Piedmont plateau and the southern Appalachian mountains and their extension westward as far as the Ozark hills.[6]

Pathology and Symptomatology.—A few or several ascarids in the bowel may produce no striking symptoms, or they may cause marked pathologic change and symptoms. In transit through the lungs the larvae in large numbers produce multiple petechial hemorrhages, usually provoke a cellular reaction in the alveoli and bronchioles and may produce a consolidation of the lobules suggesting bronchial pneumonia. This disease syndrome is called *Ascaris* pneumonitis. The most frequent complaint of patients with intestinal ascariasis is an acute colicky pain in the pit of the stomach, although indigestion, loss of appetite and nausea are frequent. At times the worms are passed spontaneously *per rectum,* are vomited or emerge through the external nares. In small children, several may become inextricably entangled in a writhing mass and produce an acute obstruction of the ileum (Fig. 129), or a single worm may enter the common bile duct or the appendiceal lumen or may perforate the bowel wall. Adult worms have been found in the fallopian tubules and in the pleural cavity. Even though they may produce no obstructive or traumatic damage, their by-products are absorbed by the system and produce neurotoxic symptoms. Furthermore, *Ascaris*-infected children are mentally less alert than uninfected controls.[6,15]

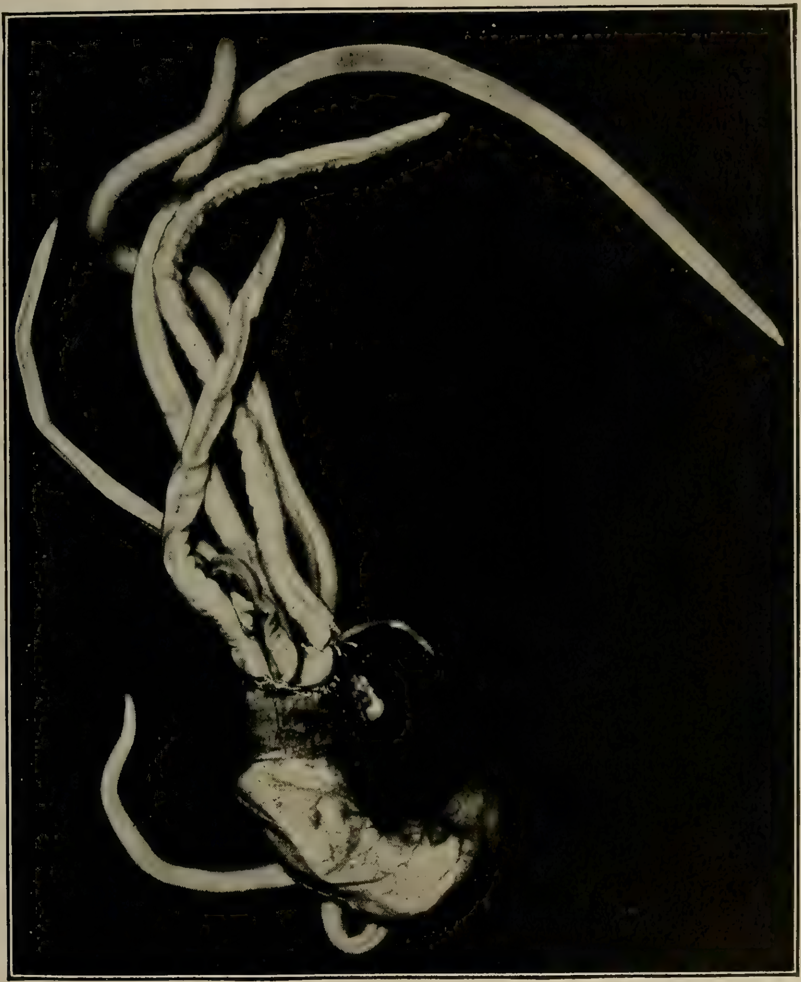

Fig. 129.—*Ascaris lumbricoides* in the appendix of a six year old child, with a preoperative diagnosis of "acute abdomen." At operation, in addition to the worms in the appendix, nine had escaped into the peritoneal cavity. The patient died of peritonitis. (From Craig and Faust's *Clinical Parasitology*, through the courtesy of Dr. Samuel Field and Dr. Robert Strong.)

Diagnosis and Prognosis.—Diagnosis is based on the recovery of the characteristic eggs in the patient's feces. These are sufficiently numerous, even when a single female worm is present, to allow recovery without concentration technics. Infrequently only one or more males are present, in which case no specific pretreatment diagnosis can be made. The prognosis is good, except when overwhelming numbers of larvae are migrating simultaneously through the lungs and when the adult worms obstruct the digestive tract and its diverticula or perforate the bowel wall.

Treatment.—In the presence of acute intestinal obstruction, no food, purgatives or anthelmintics should be administered. Surgical removal of the worms is frequently indicated.

1. *Hexylresorcinol* (*caprokol*) *Crystoids.*[6,11,22]—Preparation: Hard gelatin capsules, each containing 0.1 or 0.2 Gm. Therapeutic dose: 1 Gm. for adults and children over ten years of age; 0.4 to 0.6 Gm. for children under six years; 0.8 Gm. for children six to ten years of age. Administration: The entire prescription is taken by mouth at one time in the morning on an empty stomach. No pretreatment purgation is required, although it is advised to free the bowel so that the anthelmintic may act readily on the worms. Likewise, post-treatment saline purgation (Glauber salts, 15 Gm. in a glass of water) is desirable to remove dying and disintegrating worms. Precautions and Contraindications: The capsules must be swallowed without being crushed in the mouth. Food is prohibited for four to five hours. Toxicity: None apparent when administered as recommended. Efficiency: 90 per cent or more in worm removal; usually produces cures with a single course of treatment.

2. *Santonin.*—Preparation: Powdered drug, mixed with calomel. Therapeutic dose: 0.06 to 0.2 Gm., combined with 0.2 to 0.3 Gm. of calomel. Administration: By mouth as a single dose in the morning on a full stomach, followed within two hours by saline purgation. Precautions and Contraindications: Must never be administered on an empty stomach or with absorbable oils. Toxicity: Especially harmful to the central nervous system and organs of special sense, particularly the optic nerve.[8] May produce severe enteritis, headache, vertigo, mental confusion, ocular disturbances, hallucinations, convulsions, extreme weakness, prostration, drowsiness and even coma. Efficiency: Rarely, if ever, vermicidal. Hall and Augustine[18] assigned a 27 per cent worm-removal rating to santonin.

3. *Oil of Chenopodium.*—Preparation: Volatile distilled oil of *Chenopodium ambrosioides* var. *anthelminticum,* containing 60 to 80 per cent ascaridol, in gelatin capsules or on a teaspoon. Therapeutic dose: 1.5 to 3 cubic centimeters for adults; 1.5 to 3 minims per year of age for children. Administration: Given in the morning on an empty stomach, in three divided doses, one-half hour apart; preceded the previous night by Glauber salts purgation and followed in one or two hours by Glauber salts purgation, since the drug inhibits peristalsis. Precautions and Contraindications: The patient should refrain from taking absorbable fats and alcoholic drinks for at least forty-eight hours preceding treatment. This drug should not be prescribed for patients with nephritis, organic heart disease, ulceration of the bowel, hepatic cirrhosis or acute atrophy of the liver. It should not be administered except under the immediate supervision of a physician who understands its dangers. Toxicity: The drug is absorbed by the intestinal wall and excreted by the lungs and kidneys over a long period. The therapeutic dose is near the minimum lethal dose and usually provokes marked gastrointestinal symptoms, vertigo, headache, tinnitus aurium and, at times, complete prostration and coma.[6,10,11] Efficiency: Very high, with a worm-removal rate of about 95 per cent.

Prevention.—Therapy alone has little effect in reducing ascariasis in an *Ascaris* family or an *Ascaris* environment. Sanitary toilets should be available for all children as well as for adults and should be used methodically. Only with education along this line can the infection be controlled.

Hookworms (Necator americanus, Ancylostoma duodenale, Ancylostoma braziliense), Producing Hookworm Infection or Hookworm Disease.—**Etiology and Biology.**—The adult hookworms are pin sized and grayish (Fig. 130), at times with a blood-red central core. The females are bluntly pointed at their caudal end; the males have a caudal umbrella-like expansion. *Necator* has a buccal capsule armed with cutting plates; *Ancylostoma,* one with two pairs of teeth on its upper aspect. With this armament the worms attach themselves to the mucosa of the middle levels of the small bowel. They suck blood out of the villi and digest the tissue cells for use as food. The females each lay a few thousand eggs per day. These eggs are ovoidal, thin shelled and hyaline, measure about 60 by 40 microns and usually contain embryos in the early stages of cleavage when evacuated in the feces (Fig. 138, 3).

If deposited on moist, sandy humus in a warm environment, hookworm eggs hatch in twenty-four to forty-eight hours, and the emerging larvae feed ravenously on organic debris. They grow in size, molt, feed and grow again and then become transformed into more elongate postfeeding larvae (*filariform larvae*), which are infective for man. They penetrate the skin of the bare feet or other exposed areas of the body, burrow down to the cutaneous capillary beds and are then transported *via* the right chambers of the heart to the lungs. Here they break out into the air sacs, travel up the respiratory tree over the epiglottis and are swallowed. In the small bowel each worm develops a head capsule, attaches itself to the mucosa and in five to six weeks following exposure develops into an adult worm.[6]

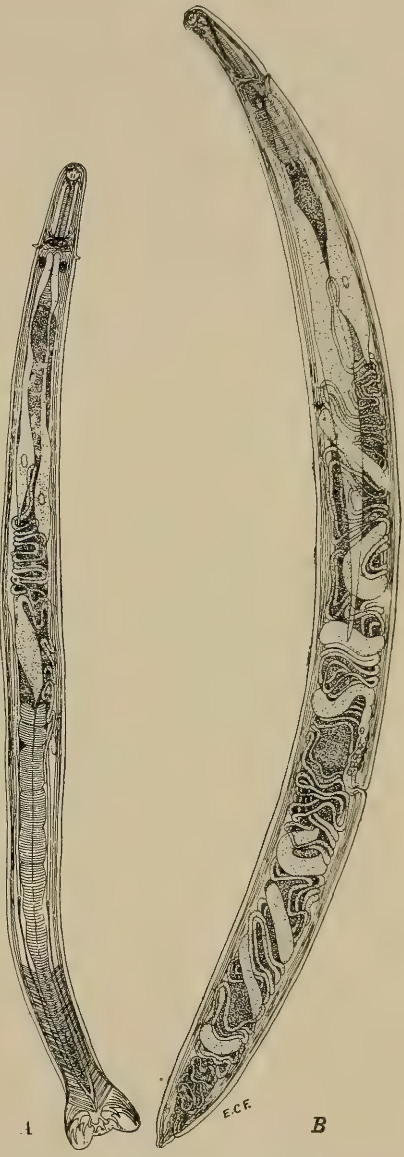

FIG. 130.—Adult hookworms (*Ancylostoma duodenale*): *A*, male; *B*, female (× 20). (From Faust's *Human Helminthology*, adapted from Looss.)

Epidemiology.—Hookworms are found throughout the warm, moist regions of the world. *N. americanus* is the prevalent species in the Western Hemisphere and in the Old World south of 20 degrees north latitude;

A. duodenale is the predominant species in northern Africa, southern Europe and central Asia; *A. braziliense* is found as a subsidiary human infecting agent throughout the Tropics. Of the three species, it alone is harbored by reservoir hosts, dogs and cats. The soil is "seeded" with eggs discharged in feces. The hatched larvae develop in the soil to the infective stage and are then picked up by man when his unprotected skin comes in contact with larvae in the infective stage.[6]

Pathology and Sympatomatology.—Hookworms produce hookworm infection but not necessarily hookworm disease. The latter is due to several factors, usually including poor nutrition and a low threshold of resistance, and always requires several hundreds of the worms attached to the bowel and day by day pumping out blood in excess of blood regeneration. Thus, there is a graded series of cases, from those in which so few worms are present as to produce no symptoms to those in which a sufficient number of worms are present to produce profound pathologic change and symptoms. Constant reinfection in endemic foci increases the severity of infection.

The blood picture of hookworm disease typically is that of a hypochromic, microcytic type of anemia, at times with eosinophilia. The red cells may be reduced to less than 1,000,000 per cubic millimeter and the hemoglobin concentration as low as 10 to 15 per cent. Rarely there may be aplastic anemia.[6]

At the site of invasion of the skin there is usually an ulcerated lesion referred to as "ground itch." The lungs may exhibit atypical bronchial penumonia when large numbers of larvae are migrating through the pulmonary capillaries into the air sacs. The feces show indications of intestinal hemorrhage or may assume a tarry consistency even before the females begin to lay their first eggs. After each worm has fed for a time on the mucosa of the small bowel, it abandons the site, which becomes a weeping, phagedenous ulcer, into which pyogenic bacteria enter. There are general digestive disturbances, with false hunger pains and frequently geophagia. The loss of blood and the greatly lowered level of metabolism are responsible for the dry, harsh skin and dry hair, the emaciation, the enlarged abdomen, the palpitation of the heart, the worried facies, the endocrine dysfunction and both physical and mental "laziness." Porter[28] (1937) has shown that the following physiologic adjustments are made to compensate for the loss of hemoglobin: (1) augmented vital capacity of the lungs; (2) increased tolerance of tissue cells to oxygen want; (3) cardiac hypertrophy, and (4) reduction in volume of peripheral blood flow.

Diagnosis and Prognosis.—The specific diagnosis is made on the finding of hookworm eggs (Fig. 138, 3)—rarely of first stage larvae—in the patient's feces. The degree of infection is determined by the physical findings, the blood picture and the number of eggs in the feces. The prognosis is good in most cases, even with a heavy infection, provided specific treatment and a well balanced, nutritious diet are given.

Treatment.—(A) *Supportive treatment,* preceding and during specific treatment: With profound anemia it is at times desirable to give two or three pretreatment transfusions. However, usually the administration of ferrous sulfate, ferrous carbonate (Blaud's pills) or iron ammonium citrate, in addition to a nutritious diet, will raise the hemoglobin and increase the erythrocytes to a satisfactory level so that specific therapeusis may be safely instituted.

(B) *Specific treatment:* 1. *Tetrachlorethylene.*—Preparation: In soft gelatin capsules [6,10,11,26] of 1 or 0.5 cubic centimeter each, or on a teaspoon with sugar. Therapeutic dose: 3 cubic centimeters for an adult; 3 minims per year of age for children, up to the adult dose. Administration: After saline purgation the night before anthelmintic medication (Glauber salt, ½ ounce in a glass of water, is particularly recommended, because it dissolves mucus from around the heads of the worms), the drug is given in one dose, in the morning on an empty stomach (black coffee or tea excepted), followed in two hours by post-treatment saline purgation; no food is permitted until adequate purgation has been obtained. Precautions and Contraindications: It is desirable to omit absorbable fats and alcohol from the diet for forty-eight hours before treatment, to prevent absorption of the drug, which is not appreciably soluble in water. Toxicity: Practically nil[23] when recommendations are carried out; there may be a slight burning pain in the pit of the stomach and some dizziness, which is lessened if the patient remains in bed during treatment and refrains from taking carbonated drinks.[6] Efficiency: About 90 per cent worm-removal rate; 62 per cent cure rate.

2. *Carbon Tetrachloride.*—Preparation: In soft gelatin capsules of 1 or 0.5 cubic centimeter each, or on a teaspoon with sugar. Therapeutic dose: 3 cubic centimeters for an adult;[19] 3 minims per year of age for children, up to the adult dose. Administration: The same as for tetrachlorethylene (aforementioned). Precautions and Contraindications: Absorbable fats and alcohol should be omitted from the diet for forty-eight hours before treatment; this drug should not be presecribed in cases of acute alcoholism, cirrhosis of the liver or renal or respiratory disease or during a fever; pretreatment administration of calcium lactate or calcium pluconate will prevent the possibility of guanidine intoxication.[25] The preparation is contraindicated for mixed infections with hookworms and *Ascaris*, but if 0.3 cubic centimeters of oil of chenopodium is added to 2.7 cubic centimeters of carbon tetrachloride for an adult dose, the combined anthelmintic is relatively safe and efficient. Toxicity: Unless adequate precautions are taken, this drug is very toxic,[10] producing convulsions, hemorrhage and necropsy evidence of rapid fatty degeneration of the liver and of cloudy swelling and fatty infiltration of the kidneys. Efficiency: About 95 per cent worm-removal rate.

3. *Thymol.*—Preparation: Powdered or finely granular crystals. Therapeutic dose: 1 to 2 Gm. (15 to 30 grains) in each of two or three divided doses (maximum dose, 4 Gm., or 60 grains) for an adult,[5] correspondingly smaller doses for children, with lactose or sodium bicarbonate. Administration: After saline purgation the night before, the drug is administered in the morning on an empty stomach in two or three divided doses one-half hour apart, followed within two hours by saline purgation. Precautions and Contraindications: No absorbable fats or alcohol is allowed for forty-eight hours preceding treatment. The drug should not be administered in cases of nephritis or of epilepsy. Toxicity: Thymol irritates mucous membranes; it first stimulates, then depresses the central nervous system; it produces headache, tinnitus aurium, and vertigo, irritates the kidneys and occasionally causes subnormal temperature and collapse.[10,11] Efficiency: 88.6 per cent worm-removal rate.

4. *Hexylresorcinol crystoids,* administered in the amount and in the same way as for ascariasis (*vide supra,* p. 604), has a worm-removal rate of about 75 to 80 per cent.[22] For combined hookworm and *Ascaris* infections in children or the debilitated, this is the drug of choice, since its administration may be safely repeated every few days until the infection is reduced to a nonclinical level.

Prevention.—Specific treatment of all infected persons is important, in order to reduce the amount of infection in the soil. While hookworm disease in man can be prevented by care not to expose the skin, especially that of the feet, to infectious soil, this is not usually practical in the population groups in which the disease is most heavily endemic, *i. e.,* the poorer classes in the Tropics. The fundamental problem consists in the sanitary disposal of human feces. Where there is sanitary sewerage the problem of disinfecting the soil has been solved. The use of pit privies or bored hole latrines has been found equally effective, wherever all persons in a group have been compelled to use this sanitary convenience regularly.[1]

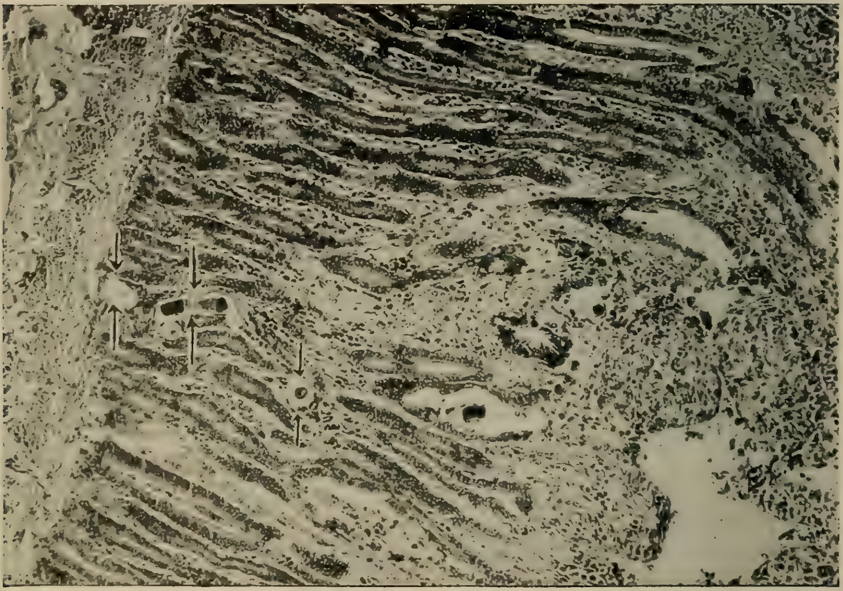

FIG. 131.—Parasitic female *Strongyloides stercoralis* (indicated by arrows) deep in mucosa of an experimentally infected dog (× 100). (After Faust, in *Archives of Pathology.*)

Strongyloides stercoralis, Producing Strongyloidiasis.—Etiology and Biology.—*Strongyloides stercoralis* is a small roundworm having both a parasitic and a free-living phase. The parasitic female is a delicate thread worm, just visible to the unaided eye. She lives typically in the villi and glands of the intestinal mucosa (Fig. 131), most commonly at the levels of the duodenum and the upper part of the jejunum, where she lays partially embryonated thin-shelled eggs, which hatch in the tissues to produce first stage (rhabditiform) larvae, which burrow out to the lumen of the bowel and are passed as active larvae in the feces (Fig. 138, 4).

On she ground, these larvae feed, grow and may develop directly into infective-stage filariform larvae (like the hookworm), or they may be transformed into free-living adults, which mate and produce a free-living progeny. Under optimum conditions the free-living propagation may be continued indefinitely, but usually after a single free-living generation infective-stage larvae are produced. These enter the skin and migrate *via* the lungs to the bowel, just as the hookworms do.[6]

At times there is a third type of development, in which first stage larvae in transit down the bowel develop immediately into infective-stage larvae and thus may penetrate the intestinal wall and by an internal route reach the lungs in transit back to the intestine (*hyperinfection*) or may infect the perianal skin (*perianal autoinfection*). The hyperinfective method is the one responsible for maintaining infection in patients for many years after they have left infected environments.[12]

Epidemiology.—Strongyloidiasis is prevalent throughout the warm climates of the world, but autochthonous disease in the United States has presumably been found as far north as New York City. Infection results from exposure of the unshod feet (or other unprotected areas of the skin) to infectious soil. Man is the only known host entirely suitable for this infection.

Pathology and Symptomatology.—There is an appreciable needling sensation on the exposed skin at the time the infective stage larvae are entering and for a week or so thereafter itching, with irritation of the site if it is rubbed. About a week after exposure there is usually a low grade hacking cough. After four weeks or more, when larvae first appear in the stool, there may be a mucous diarrhea. In some patients diarrhea alternates with constipation; in others there is an uncontrollable watery-mucous discharge, rarely with blood; in many patients there is no appreciable digestive dysfunction. Usually the worms are confined to the mucous coat of the intestine by an infiltration of round cells and eosinophils. In occasional cases of fatal termination the migrating larvae may break down the host's defense mechanism, invade the circulation and produce a parasitemia. The infection is long lived and is frequently maintained by hyperinfection. With old chronic disease there may be no marked intestinal symptoms, but a depressed neurotoxic state may exist. The blood picture at first shows a leukocytosis with pronounced eosinophilia (a count up to 75 per cent or more). Later, there are neutropenia and monocytosis, with greatly reduced eosinophilia. There may be erythropenia, but this is not pathognomonic.[6]

Diagnosis and Prognosis.—Specific diagnosis consists in the recovery in direct fecal films or by concentration technics of the first stage larvae (Fig. 138, 4) (occasionally the infective-stage larvae), which require differentiation from the similar stages of hookworms. In most cases the prognosis is good, provided efficient therapeusis is carried out.

Treatment.—Only one specific therapeutic agent is known, namely, *gentian violet medicinal*.[6,10,11] However, the drug must reach the female worms in the bowel wall in lethal amounts before their eradication can be secured. Preparation: ½ grain (0.03 Gm.) 1½- or 2-hour Enseals or Seal-Ins coated pills. Therapeutic dose: 50 grains (1.5 Gm.), given over 16⅔ days. Administration: Two pills (1 grain, 0.06 Gm.), taken three times daily before meals, until 50 grains have been taken. No pretreatment or posttreatment purgation is necessary. Precautions and Contraindications: Rarely a patient with strongyloidiasis becomes nauseated and vomits after taking this drug or complains of acute intestinal distress following a few days of treatment. For these patients, as well as for those in whom one or two full courses of treatment do not produce cure, transduodenal intubation is the procedure of choice. A duodenal tube with a metal sound is introduced under fluoroscopic vision and the patient allowed to rest for a half hour to an hour. Twenty-five cubic centimeters of a 1 per cent solution of gentian violet medicinal is then slowly passed into the duodenum and the patient requested to remain quiet for an hour before the tube is removed. Some patients are not nauseated by the intubation; others vomit the solution during its instillation, during removal of the tube or shortly afterward. One intubation is usually sufficient, even when the condition is obstinate or when some of the solution has been vomited. Toxicity: Gentian violet is very irritating to the gastric mucosa and somewhat irritating to the mucous membrane of the small and large bowel, but no unfortunate sequelae have been reported from its oral administration. Efficiency: One or two courses of treatment with 50 grains in $1\frac{1}{2}$- or 2-hour Enseals or Seal-Ins coated tablets produce approximately 90 per cent cures. When the condition is refractive, the intubation technic has an equally high efficiency.

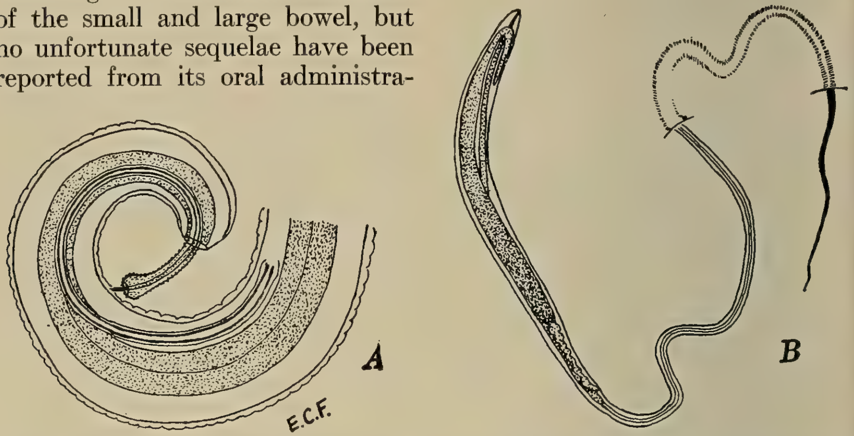

Fig. 132.—The whipworm infesting man (*Trichocephalus trichiurus*). *A*, posterior end of male, with copulatory sheath and spicule (× 35); *B*, entire female, "sewed" into the intestinal mucosa (× 6). (From Faust's *Human Helminthology*, after Yorke and Maplestone's *Nematode Parasites of Vertebrates*, courtesy of J. and A. Churchill, Ltd.)

Prevention.—In endemic areas persons are advised not to walk barefooted on the ground.

Trichocephalus trichiurus (The Whipworm or "Trichuris"), Producing Trichocephaliasis or Trichuriasis.—Etiology and Biology.—These worms have a length of 30 to 50 mm., with a capillary anterior three-fifths and a fleshy posterior two-fifths (Fig. 132). The posterior end of the male is conspicuously coiled. The worms live with their anterior ends inserted into the mucosa of the cecum, appendix, posterior level of the ileum and the ascending colon. The female lays a few thousand characteristic eggs daily; these are bile stained, measure 50 to 54 by 22 to 23 microns, are more or less barrel shaped and have a pearly white protuberance at each end (Fig. 138, 5). They are unsegmented when discharged in the feces and require a few to several weeks on moist shady ground for complete development. When the fully developed eggs are swallowed, they hatch in the small bowel, and the larvae slowly work their way down the bowel, become attached and in about three months mature and begin to oviposit.

Epidemiology.—Man is infected from ingesting the fully matured eggs, previously passed onto the ground in infected human feces. No host other than man is known. The distribution of this infection is widespread in warm climates.

Pathology and Symptomatology.—In light infections, usual in the southern part of the United States, there are rarely conspicuous intestinal symptoms, although neurotoxic manifestations may occur and there may be an 8 to 20 per cent eosinophil count. In heavy infections, digestive disorders may be apparent, with diarrhea, incomplete digestion of food, poor nutrition, emaciation and marked secondary anemia.

Diagnosis and Prognosis.—Diagnosis is always based on the recovery of the characteristic eggs in the feces (Fig. 138, 5). The prognosis is usually fair to good, but heavily infected patients should be treated with both specific drugs and nutritious food.

Treatment.—1. The only safe, efficient therapeutic agent is *leche de higuerón* (milk of the fig tree, *Ficus glabrata,* which grows in Tropical America). Preparation: This product is not available in the United States, but may be obtained from Higueronia, Cali, Colombia or Mexico, D. F., in bottled form, preserved with 1 per cent sodium benzoate. Therapeutic dose: 2 ounces (60 cc.) for adults or children. Administration: In the morning before breakfast, preferably preceded by Glauber salts purgation and high retention enemas of physiologic salt solution the night before. No post-treatment purgation is necessary. Precautions and Contraindications: None known. Toxicity: This product contains a proteolytic enzyme, ficin, which is the anthelmintic fraction. There is no evidence that it irritates or attacks intestinal mucosa or is absorbed by the bowel wall. Efficiency: High, with a worm-removal rate of 85 to 90 per cent.[4]

2. *Hexylresorcinol Crystoids.*—This anthelmintic is fairly effective in removing *Trichocephalus.* It may be administered repeatedly with safety. The therapeutic dose and method of administration are as outlined for ascariasis (*vide supra,* p. 604).[10,11]

3. *Oil of Chenopodium.*—This drug is efficient but is very toxic in therapeutic amounts (*vide supra,* p. 604). Its administration is not recommended.[10,11]

4. *Tetrachlorethylene.*—When administered as for hookworm infection (*vide supra,* p. 607), this drug is moderately effective in removing the majority of whipworms in massive infections, but it is not satisfactory for removing the worms in light infections.[10,11]

5. *Tetrachlorethylene and Oil of Chenopodium Combined.*[6]—Probably the most efficient medication available in the United States is a combination of tetrachlorethylene and oil of chenopodium in the proportion of 9 : 1. Therapeutic dose: 2.7 cubic centimeters of tetrachlorethylene, 0.3 cubic centimeters of oil of chenopodium. Administration: The night before treatment Glauber salt purgation (15 Gm. dissolved in a glass of water) is carried out, followed by a high retention enema of physiologic salt solution to clear out residual viscous feces associated with the worms. In the morning the patient remains in bed, refrains from eating and takes the anthelmintic in one dose. Two hours later Glauber salt purgation is

carried out. Precautions and Contraindications: Essentially nil except in heavily infected patients who are toxic.

Prevention.—Control of trichocephaliasis parallels that for ascariasis. Children and adults must use care not to place their fingers in their mouths after contamination with the ground. Sanitary disposal of human feces is indicated.

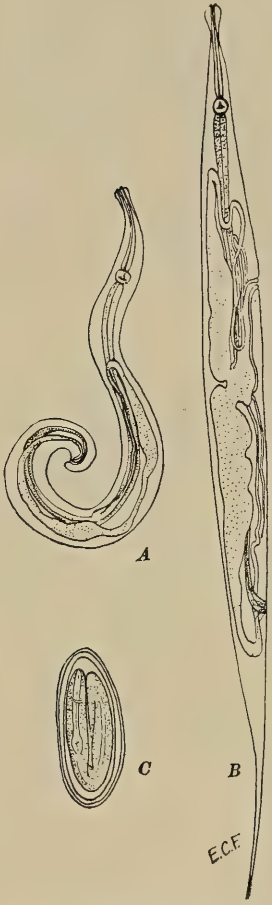

FIG. 133.—The human seatworm (*Enterobius vermicularis*). *A*, adult male (× 16); *B*, adult female (× 16); *C*, fully embryonated egg recovered from perianal swabbing (× 280). (From Faust's *Human Helminthology*; *A* and *B* after Leuckart, courtesy of Akademische Verlagsgesellschaft.)

Enterobius vermicularis (Oxyuris vermicularis, Pinworm or Seatworm), producing Enterobiasis or Oxyuriasis.—Etiology and Biology.—The males measure 2 to 5 mm. in length by 0.1 to 0.2 mm. in greatest diameter and have a coiled posterior end (Fig. 133, *A*). The females measure 8 to 13 mm. long by 0.3 to 0.5 mm. in greatest diameter, are spindle shaped and have an acutely pointed posterior end (Fig. 133, *B*). The young adults are attached to the intestinal mucosa in the region of the cecum, appendix, posterior level of the ileum and ascending colon. The gravid females loose their attachment and migrate, usually down the bowel and out of the anus into the perianal and perineal folds. In less than 5 per cent of infected persons the females lay eggs inside the bowel; characteristically they oviposit only after they have emerged from the anus, when they trail strings of eggs behind them. These eggs outside the bowel are normally fully embryonated when laid, elongate ovoidal but flattened on one side and hyaline with a fairly thick shell, and measure 50 to 60 by 20 to 30 microns (Fig. 138, 6). They are infective when taken into the mouth and swallowed, hatch in the duodenum or jejunum and in two months or less develop into adults.

Epidemiology.—Man becomes infected from ingesting the fully embryonated eggs oviposited by gravid mother worms in the perianal and perineal folds of infected persons. Soiled bed linen and night clothes, toilet seats and other contaminated objects serve as the mediums of infection. The eggs are also blown about in the air and may be inhaled and then swallowed. This infection is cosmopolitan in its distribution but is more common in family and institutional groups than in the population at large.[6]

Pathology and Symptomatology.—Although there is usually little evidence of damage to the intestinal wall, in some patients an appendicopathia develops, and on surgical removal of the appendix there is concrete evidence of profuse bleeding at the sites where the worms are attached, as well as local cellular reactions indicating that the lesions produced serve as portals of entry for pathogenic bacteria. In addition, the by-products of the worms, when absorbed, produce reflex manifestations, including nausea, vomiting and convulsions, particularly in small children.[6]

By and large, the greatest annoyance and symptoms are caused by the migration of the gravid females out of the anus, producing an almost intolerable perianal and perineal pruritus, which causes scratching of the area with resultant scarification and pyogenic infection. There is usually an accompanying nervous syndrome, with insomnia, loss of appetite and weight and frequently hysteria in female patients.

Diagnosis and Prognosis.—In less than 5 per cent of cases is the infection diagnosable by recovery of eggs in the feces. In a considerably larger percentage diagnosis is made by apprehending the worms as they crawl out of the anus or after the large bowel is flushed. The most efficient diagnostic technic is perianal swabbing for eggs (Fig. 138, 6) with a small square of thin cellophane folded over a glass rod and attached with a rubber band. Most satisfactory results are obtained when the swabbings are made in the morning before the morning stool is passed and before the bath. Even by this technic, seven daily swabbings must be made before it is safe to consider the result "negative." The prognosis is always good, provided persistent efforts are undertaken with specific therapeutic agents to eradicate the infection.

Treatment.—1. *Enemas.*—High enemas with warm water, quassia infusions or antiseptic solutions are usually helpful in removing the majority of the adult worms in the large bowel and thus provide temporary relief for the patient. However, they are rarely, if ever, curative, since they fail to eliminate the larvae and young worms in transit down the small intestine or to sterilize the eggs which are responsible for reinfection.

2. *Hexylresorcinol Crystoids.*—When prescribed and administered as for ascariasis (*vide supra*, p. 604), this anthelmintic is very efficient in removing the infection from the small bowel; but its use must be supplemented with anthelmintic enemas to evacuate the worms in the large bowel. A satisfactory supplementary treatment[13] is as follows: (*a*) the night after the oral administration of hexylresorcinol crystoids, the large bowel should be thoroughly washed out with a high, tepid water enema; (*b*) after this a retention enema of 1 : 1,000 solution of hexylresorcinol (S. T. 37, undiluted), 8 to 16 ounces (230 to 460 cc.) depending on the age of the patient, is given; this enema, to be effective, should reach the cecum and appendix and should be retained for fifteen to thirty minutes before being evacuated. The oral and rectal treatment with hexylresorcinol may need to be repeated weekly for several weeks or even months before cure is obtained. In case the retention enema produces acute colic or spasms in small children, it should be evacuated at once and the patient quieted wish a sedative (sodium amytal or sodium bromide).[10,11]

3. *Gentian Violet Medicinal.*—This therapeutic agent for enterobiasis is the most encouraging.[6,7,32] Preparation: Seal-Ins or Enseals coated tablets (4-hour), $\frac{1}{6}$ grain (0.012 Gm.) or $\frac{1}{2}$ grain (0.03 Gm.) each. Therapeutic dose: For adults, 1 grain (0.06 Gm.) three times daily for eight days followed by a week's rest and again for eight days; for children, 10 mg. ($\frac{1}{6}$ grain) daily for each year of apparent (not chronologic) age for the course of treatment. Administration: Immediately before meals or on a full stomach; no pretreatment or post-treatment purgation is necessary. Precautions and Contraindications: While most patients tolerate this

drug well, some experience griping abdominal pain, diarrhea, headache, dizziness, nausea and vomiting. (Vomiting with gentian violet medication is apparently much more common in enterobiasis than in strongyloidiasis.) The drug is contraindicated for patients suffering from "moderate or severe cardia, hepatic, renal or gastrointestinal disease."[7,32] Toxicity: Gentian violet temporarily irritates and sometimes inflames the intestinal mucosa and is an acute irritating agent for the gastric mucosa. Efficiency: Nearly 92 per cent curative provided all infected members of a group are treated simultaneously.[7,32]

Prevention.—Enterobiasis cannot be eradicated by specific treatment of only one member of an infected group of persons. All members of the group should be examined, and all for whom a positive diagnosis is made by the swab technic must be treated until seven post-treatment swab examinations give negative results. Meticulous group and personal hygiene must also be practiced, but this without intensive specific therapy is ineffectual in eradicating the infection.

Trichinella spiralis, Producing Trichinosis.—**Etiology and Biology.**—The adult "trichina" worm is a minute, almost microscopic, organism. The male measures 1.4 to 1.6 mm. by 40 to 60 microns, the female, about 3 to 3.5 mm. by 60 to 100 microns. These worms enter the human digestive tract as encysted larvae in the flesh of infected pork (rarely in bear meat), "hatch" in the duodenum and enter the mucosa of the duodenum and upper part of the jejunum. After fertilization the females burrow down to the base of the mucosa, and about seven or eight days after exposure they begin to larviposit. While some larvae are at first extruded into the lumen of the bowel, in increasing numbers they get into the mesenteric venules or lymphatic vessels and are distributed throughout the body, being finally filtered out in striped muscle, especially that poor in glycogen. Here they encyst, become encapsulated by host tissue and eventually become calcified.

Epidemiology.—Man is infected by consuming infected uncooked or inadequately cooked pork. Hogs maintain their infection from eating raw garbage containing infected hog scraps and at times from eating infected rats. This infection is widely distributed throughout the world, but is of particular importance in the United States, especially in New England, New York, Pennsylvania, Minnesota and California. In the southern part of the United States clinical trichinosis is relatively rare, although the population has considerable subclinical infection.

Pathology and Symptomatology.—The typical classic infection exhibits the following three stages: (1) the incubation period, with symptoms suggesting acute food poisoning; (2) the period of migration of the larvae, with excruciating myositis, at times diagnosed as "acute muscular rheumatism," and (3) the chronic period, following the encystation of the larvae, with respiratory and neurotoxic symptoms. In addition, pronounced edema, especially around the eyes, a remittent fever (40° to 41° C.) and, later, myocarditis are important symptoms. A pronounced eosinophilia develops about the fourteenth day and reaches its maximum (a concentration of 20 to 75 per cent or more) by the end of the third week. When the condition is grave the patient may succumb to respiratory and cardiac failure. At times the symptoms in no wise conform to the classic picture.[3,17]

Diagnosis and Prognosis.—With a history of the eating of raw or rare pork followed by an acute digestive upset and then by myositis, with elevated temperature and edema, a clinical diagnosis of trichinosis may be entertained. This is reinforced when marked eosinophilia is discovered. A specific diagnosis can be made after the first week or ten days by biopsy of a muscle strip, which may be pressed between two slides and examined or (preferably) digested in artificial gastric juice, centrifuged and examined for larvae. After the twentieth day the intradermal reaction (immediate) is positive to powdered "trichina" antigen in Coca's solution (1 : 5,000 or 1 : 10,000 dilution).[6] The prognosis is good except for patients with an overwhelming infection, those with grave neurotoxic manifestations or myocarditis and those without eosinophilia. Months or even years of invalidism may follow a severe attack.

Treatment.—Only palliative and supportive treatment are available. The patient should be placed on a bland diet and the digestive tract kept open and alkalinized. Diuretics are indicated. Sedatives should be used during acute myositis. Supportive treatment is frequently needed for the respiratory and cardiac mechanisms.[3]

Prevention.—Thorough cooking of all pork products will guarantee protection of man from the infection, or pork may be refrigerated at 50° F. (10° C.) for not less than twenty days. Eradication of the infection can be achieved only by the prevention of infection in hogs. Today, in the United States, hogs become infected most commonly by eating garbage containing uncooked infected pork scraps. Anti-rat campaigns around abattoirs have not proved effective.[6]

THE TAPEWORMS (CESTODES)

Tapeworms consist of (*a*) a "head," or scolex, by which the organism is attached to the tissues of its host; (*b*) a "neck," which is unsegmented but constitutes the portion from which future development of the worm originates, and (*c*) a series of few to many "segments," or proglottis, which may successfully be distinguished as immature, mature and gravid as they are more distally removed from the neck. Tapeworms lack a digestive system. Each mature proglottid contains a complete set of both male and female reproductive organs (*i. e.*, it is hermaphroditic). The gravid proglottid is a postmature one containing little else than mature and maturing eggs *in utero*. The mature eggs each contain a six-hooked (hexacanth) embryo.

Taenia saginata (Beef Tapeworm) and Taenia solium (Pork Tapeworm) Producing Teniasis.—**Etiology and Biology.**—These are the largest of the human tapeworms. *T. saginata* (Fig. 134) has a more or less rhomboid "head," with four conspicuous suckers, and a depressed rostellum which lacks hooklets; a "neck" region 2 to 3 centimeters long, and a series of 1,000 or more proglottids, of which the distal one-third are usually gravid. The worm measures 5 to 25 meters or more in length. Each gravid proglottid is two or three times as long as it is wide and has a uterus with fifteen to twenty (usually about eighteen) main lateral arms on each side of the main uterine stem. The eggs are subspherical, measure 31 to 43 microns in diameter and have a thick, mosaic-like outer shell, a thin inner shell and a hexacanth embryo within. These eggs, which cannot be distinguished from those of *T. solium,* may be recovered in feces but usually remain unshed within proglottids passed *per anum.* When the eggs are discharged on the soil on which cattle graze and are ingested by cattle, they hatch in the small bowel and the embryos migrate to skeletal muscles, where in about three months they develop into ovoidal, milky white cysticercus larvae. When man consumes raw or inadequately cooked beef containing the infection, the cysticerci develop into adult tapeworms in his small intestine. The incubation period in man is about ten to twelve weeks.[6]

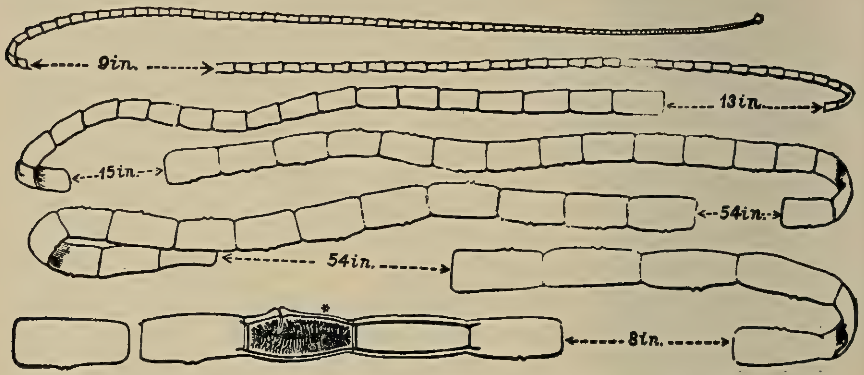

Fig. 134.—The beef tapeworm (*Taenia saginata*). Complete worm, showing "head," "neck" and immature, mature and gravid (*) proglottids (natural size). From Faust's *Human Helminthology,* after Leuckart's *Parasiten des Menschen,* courtesy of Akademische Verlagsgesellschaft.)

T. solium has a "head" with four suckers and a somewhat raised rostellum surmounted with hooklets, a rather short, thick "neck" and considerably less than 1,000 proglottids. It measures 2 to 7 meters in length. The gravid proglottid is not more than one and one-half times as long as it is wide and contains a uterus with seven to thirteen (usually nine) main lateral branches on each side of the main stem. The eggs (Fig. 138, 7), which cannot be distinguished from those of *T. saginata,* are infective for hogs (and for man). In hogs the cysticerci develop in the skeletal musculature. Man acquires infection from the adult worm from ingesting raw or inadequately cooked pork. When man accidentally ingests the eggs, he may acquire cysticercosis, which may develop in any organ or tissue of the body.[6]

Epidemiology.—Infections by these parasites are prevalent in populations eating raw or rare beef or pork. Man acquires the adult *T. saginata* or *T. solium* infection from such meat, and he may also acquire pork cysticercosis either by ingestion of the eggs of the pork tapeworm in material contaminated by egg-containing feces or, at times, by an internal autoinfection with this worm. Man is the only definite host of these two worms.

Pathology and Symptomatology.—Toward the end of the incubation period the patient manifests false hunger pains and usually a more or less pronounced diarrhea. There are loss of weight and a dyspeptic syndrome. The blood stream shows some eosinophilia and leukocytosis. Later there may be leukopenia and appreciable erythropenia. Neurotoxic symptoms usually manifest themselves in chronically infected patients.

The pork cysticercus (*C. cellulosae* or *C. racemosus*) usually produces a painless involvement of the subcutaneous tissues or somatic musculature. Almost invariably some cysts also lodge and develop in the ventricles or envelops of the brain, on the heart valves or in the orbit. After several months, when these latter cysts begin to die, they set up cellular reactions of grave significance. When the brain is involved there is commonly a syndrome of Jacksonian epilepsy.[6]

Diagnosis and Prognosis.—Diagnosis of the adult *Taenia* infection is made by recovery of the characteristic eggs (Fig. 138, 7) in the feces or of the proglottids passed *per anum*. Since specific diagnosis cannot be made from the eggs alone, fresh, unpreserved proglottids should be obtained, compressed between two slides and examined with the naked eye or under a reading glass to determine the number of main lateral arms of the uterus on each side of the main stem (*i. e.*, seven to thirteen for *T. solium*, fifteen to twenty for *T. saginata*). In beef tapeworm infection the prognosis is usually good to fair without specific therapy and excellent with eradication of the worms. In pork tapeworm infection the potential complication of cysticercosis makes the prognosis more difficult.

Treatment.—(A) *For Intestinal Teniasis*: The object of treatment is to remove the complete worm, including the "head," for if all but the "head" is removed, a complete new worm is usually regenerated in about three months. Decoctions of fresh pumpkin seed or quassia infusion do not remove the "head" and are, therefore, useless therapeutic agents.

1. *Oleoresinus aspidii* (male fern).—Preparation: The oleoresin (U.S.P.) or the extract (B.P.) is obtained from the rhizomes and stipes of *Dryopteris* (synonym, *Aspidium*) *filix-mas*. The oleoresin, when fresh, contains about 24 per cent of filicin, the effective anthelmintic principle. Therapeutic dose: 10 to 20 minims (0.6 to 1.2 cc.) in each of three divided doses (adults); 1 minim per year of age for each of three divided doses (children). Administration: (*a*) For forty-eight hours preceding treatment the patient should refrain from taking alcohol or absorbable fats and should take only a semiliquid diet the day before treatment. That night ½ ounce (15 Gm.) of Glauber salts in a glass of water is taken to clean out the bowel. The next morning the patient remains in bed and omits breakfast. At 7, 7:30 and 8 A.M. the divided doses of the drug are taken in capsules or on a teaspoon with sugar. At 10 A.M. a follow-up Glauber salt purge is taken. No food is allowed until copious evacuations have been obtained. These are collected and examined carefully for the "heads" of the worms. (Usually infections are single, but occasionally they are multiple.)

(*b*) *Oleoresinus aspidii* may also be administered in a single dose by mouth or by transduodenal intubation. After purgation the night before, the following prescription is recommended: oleoresinus aspidii, 8 Gm.; mucilage acacia, 30 cubic centimeters; distilled water, 30 cubic centimeters; Glauber salts, saturated solution, 30 cubic centimeters. No post-treatment cathartic is administered.[6,10] Precautions and Contraindications: Oleoresinus aspidii (or the extract) should not be prescribed for patients who are profoundly anemic, for the debilitated, for the aged, for infants or for pregnant women. Toxicity: Therapeutic doses may produce headache, vertigo, nausea, vomiting, severe abdominal colic and diarrhea; occasionally bilirubinemia, jaundice, albuminuria and dyspnea, and rarely convulsions, loss of reflexes, optic disturbances and respiratory and cardiac failure. However, if pretreatment and other indicated precautionary measures are carried out, these ill effects should not appear.[6,10,11] Efficiency: When the patient has been properly prepared for treatment, about 90 per cent efficiency in complete removal of the worm may be expected.

2. *Carbon Tetrachloride.*—As administered for hookworm infection (*vide supra*, p. 607), this drug has been found by some therapeutists to have a high efficiency, possibly as high as that of oleoresinus aspidii.[29] It is probably the most efficient drug available when fresh oleoresinus aspidii is not obtainable. However, it is possibly somewhat more toxic, and has the distinct disadvantage of destroying the head as well as most of the proglottids, so that it is impossible to determine from the post-treatment stools whether the treatment has been satisfactory.

3. *Pelletierine.*—This tæniacidal drug has been in use in Egypt since the sixteenth century B.C. Preparation: Pelletierine tannate, a tasteless, hydroscopic, yellowish powder, is preferred by American physicians. Therapeutic dose: 0.25 to 0.5 Gm. (4 to 8 grains). Administration: Given as a decoction on an empty stomach, followed in two hours by saline purgation. Precautions and Contraindications: No alcohol should be taken for forty-eight hours before and twenty-four hours after treatment. Toxicity: Therapeutic doses may cause intestinal colic and diarrhea, headache, vertigo, drowsiness, vomiting and diplopia. Efficiency: About 35 per cent.[30]

(B) *For Cysticercosis cellulosae:* There is no known chemotherapeutic procedure that is specific. Surgical removal of the cysticerci is indicated when they are in an operable site.

Prevention.—This consists in (1) sanitary disposal of human feces, including community sewage; (2) care not to eat beef or pork inadequately cooked, and (3) meticulous personal hygiene when handling feces containing the eggs of *T. solium*, to prevent cysticercosis cellulosae.

Diphyllobothrium latum (Broad Fish Tapeworm, the Bothriocephalus latus of older textbooks), Producing Diphyllobothriasis.—Etiology and Biology.—The "head" of this worm differs in shape from that of the other tapeworms parasitic in man, in that it is spatulate (Fig. 135) and lacks the four characteristic sucking cups. Instead, it has a pair of bothria, or sucking grooves. The proglottids have a patent uterine pore, through which immature eggs are discharged. Thus, there are no distinctly gravid proglottids. The entire worm measures from 3 to 10 meters. The eggs discharged are broadly ovoidal and operculate, measure 70 by 45 microns and contain a densely granular mass of cells (Fig. 138, 8). To proceed with development, they must be deposited in fresh water. The mature egg hatches in the water and sets free a ciliated hexacanth embryo, which may then be ingested by a water "flea" (*Diaptomus, Cyclops*). The first-stage larva develops in the body cavity of this water "flea." When small fresh water fishes eat these infected water "fleas," they acquire an infection in their flesh. Usually these are eaten by large fishes, like the pike, pickerel, bass, trout and salmon, which, in turn, acquire a flesh infection. When man consumes the uncooked or inadequately heated flesh of these fishes, he acquires the worm, which matures in his small intestine in five or six weeks.[6]

Epidemiology.—This infection is confined almost exclusively to the north temperate and subarctic regions of the world. It is common in northern

Europe and the U.S.S.R. and has developed to considerable proportions in northern Michigan, northern Minnesota and the adjacent lake regions of Canada. From endemic foci infected fish are shipped to many centers in the United States. The most heavily infected persons in North America are those of Scandinavian descent and Polish Jews. In Winnipeg Jewish housewives are frequently infected from tasting "gefüllte fisch" before it is cooked, whereas their families are usually uninfected. Man is the only important definitive host of this tapeworm. He contaminates rivers and lakes with his feces, either directly or through the emptying of city sewage into these bodies of water. He infects himself from eating inadequately cooked fish.[6]

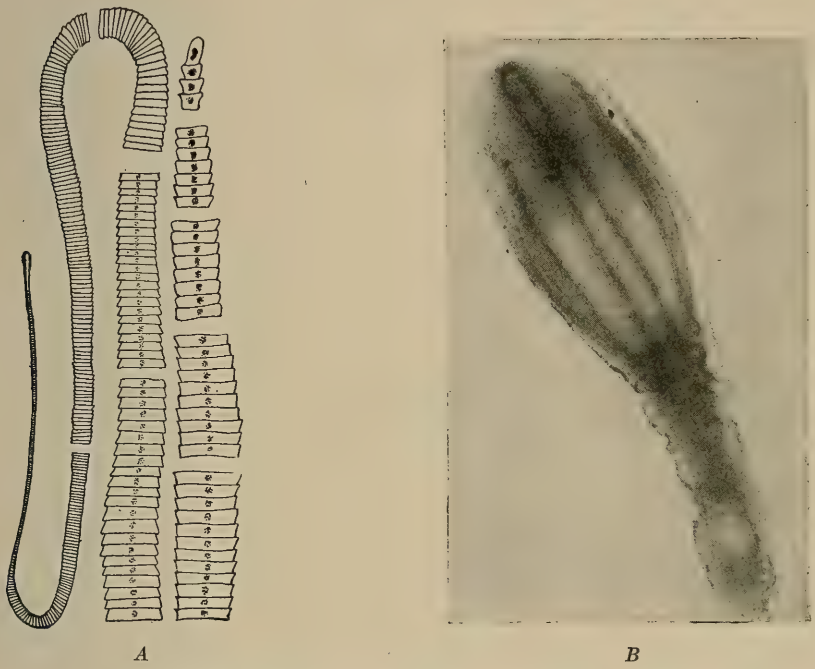

Fig. 135.—The broad fish tapeworm (*Diphyllobothrium latum*). *A*, entire worm (×2/3); *B*, head, showing lateral suctorial grooves (bothria). (From Faust's *Human Helminthology*; *A*, adapted from Leuckart's *Parasiten des Menschen*, courtesy Akademische Verlagsgesellschaft; *B*, after Magath, courtesy of *Amerizan Journal of Tropical Medicine*.)

Pathology and Symptomatology.—The symptoms produced by *D. latum* are not essentially different from those of intestinal teniasis, namely, digestive disturbances (with diarrhea, loss of appetite and loss of weight), neurotoxic manifestations and, at times, erythropenia. This worm has been accused of causing a macrocytic hyperchromic anemia, but Birkeland[2] has found that this association occurs in Europe mostly in the Finnish people, who appear to have a constitutional predisposition to pernicious anemia. Infection with the worm is believed to be a secondary factor which in some persons lowers the threshold of resistance to a level where the erythropoietic equilibrium is disturbed and the anemia is precipitated. Wardle and Green[31] have evidence that unsaturated fatty acid from the worm may be the causative factor. With removal of the worms the equilibrium is frequently reëstablished. In North America there is no authentic published record of pernicious anemia associated with a locally acquired *D. latum* infection.

Diagnosis and Prognosis.—Diagnosis is always based on recovery of the characteristic eggs (Fig. 138, 8) in the patient's feces. With specific treatment and removal of the worms, the prognosis is always favorable.

Treatment.—1. *Oleoresinus aspidii,* as recommended for intestinal teniasis (*vide supra,* p. 617).

2. *Carbon tetrachloride,* as recommended for hookworm infection (*vide supra,* p. 607).

Prevention.—This consists in (1) sanitary disposal of human excreta, including city sewage; (2) prohibition of the shipment of all fish from endemic foci during the late summer and early fall, when the fish is most heavily infected, and (3) thorough cooking of all fresh water fish.

Hymenolepsis nana (Dwarf Tapeworm), Producing Hymenolepiasis.—Etiology and Biology.—This is the smallest tapeworm living in man. It measures only 2.5 to 4 centimeters in length by 1 mm. in maximum diameter. The minute "head" possesses four suckers and a rostellum with a crown of hooklets. The worm lives singly or in multiples of a few to many dozens or hundreds attached to the human small bowel. The eggs are set free by the gradual disintegration of the distal-most proglottid of each worm and are discharged in the feces. They (Fig. 138, 9) are spherical, thin shelled and hyaline; measure 30 to 47 microns in diameter, and have an inner shell much smaller than the outer and provided with a pair of polar thickenings, from each of which four to eight long, delicate polar filaments are extended into the space between the inner and the outer shell. The embryo within the inner shell is typically hexacanth. The eggs require no special intermediate host. When swallowed by man, they hatch in his duodenum or jejunum, and the embryos enter his villi, where they are transformed into true larvae, with "heads" like the adult worm. The larvae then leave the villi, become attached to the intestinal mucosa and in about two weeks develop into adult worms.[6]

Epidemiology.—Dwarf tapeworm infection has a cosmopolitan distribution but is more common in warm than in cold climates. It is more prevalent in children than in adults. In the southern part of the United States it is the most common of all human tapeworm infections. It tends to be familial and institutional, like oxyuriasis (*vide supra,* p. 612). While a type of *Hymenolepsis* morphologically indistinguishable from *H. nana* commonly parasitizes the mouse, the murine type infects man with great difficulty. Hence, man is responsible for his own infection.

Pathology and Symptomatology.—Although patients harboring this worm may not present any distinct symptoms, even a few worms may produce systemic toxemia with appreciable anemia. At times there may be abdominal cramps, with or without diarrhea, dizziness, insomnia and loss of appetite, and, occasionally, convulsions or epilepsy in children. An eosinophil count of 8 to 16 per cent may be present.

Diagnosis and Prognosis.—Diagnosis is based on the recovery of the characteristic eggs (Fig. 138, 9) in the feces. These require differentiation from the larger eggs of the rare human tapeworm *Hymenolepis diminuta,* which lack the polar filaments. With specific treatment the prognosis is almost invariably favorable.

Treatment.—1. *Oleoresinus aspidii,* as recommended for intestinal teniasis (*vide supra,* p. 617).

2. *Caprokol,* as recommended for ascariasis (*vide supra,* p. 604). This drug is especially useful for administration to small children. Although it it not as efficient as oleoresinus aspidii, it is essentially nontoxic; its administration is much simpler, and repeated treatments may be given without danger.

Prevention.—This is a matter of personal and group hygiene. Infected patients should be treated until cured, and their underclothing, night clothes and bed linens should be changed often and thoroughly boiled.

Other Tapeworms Infecting Man.—The following tapeworms have on occasion been found in man: *Hymenolepsis diminuta,* commonly harbored by rats and requiring as an intermediate host an insect which, of accidentally ingested by man, produces human infection; *Dipylidium caninum,* commonly parasitizing dogs and cats and transmitted by their fleas; *Bertiella studeri,* a monkey parasite in the Tropics, and species of *Raillietina,* which are commonly found in rats.[6] These set us symptoms similar to those described for *Hymenolepis nana.* Treatment consists in the administration of oleoresinus aspidii, as recommended for intestinal teniasis (*vide supra,* p. 617).

THE FLUKES (TREMATODES)

Flukes are more or less ovoidal or elongated ovoidal organisms, usually flattened dorsoventrally. Most species are hermaphroditic, but the blood flukes are diecious. The man-infecting flukes have a complicated life cycle, involving three or more distinct generations and requiring an appropriate species of snail (or other mollusk) as the first intermediate host. From the snail, the organism in the infective stage may directly infect man (blood flukes), or it may require a second intermediate host as the vehicle for transfer to man, the definitive host. In the Tropics and the Orient there are many fluke infections which are of primary clinical and public health importance, but with the exception of fascioliasis (sheep liver fluke disease) none are autochthonous in North America.[6]

The Schistosomes (Blood Flukes), Producing Schistosomiasis (Bilharziasis of British texts).—Etiology and Biology.—Three species of blood flukes are common parasites of man throughout large areas of the world, *viz.,* *Schistosoma mansoni* and *Schistosoma japonicum,* both of which produce intestinal and hepatic lesions, and *Schistosoma haematobium,* which produces lesions primarily confined to the bladder and pelvic organs and tissues. Only the former two species will be considered here.

The adult blood flukes are delicate worms which live typically in portal bloodvessels, including both the mesenteric venous circulation and the intrahepatic portal system. The males are cylindroidal and have a long ventral trough (the gynecophoral canal), in which they hold the delicate capillary females during insemination and egg laying. The Oriental species (*S. japonicum*) has a predilection for the venules draining the small bowel; Manson's blood fluke (*S. mansoni*) more commonly lives in the venules draining the large bowel. The eggs of these worms are deposited by the females in the small venules next to or within the bowel wall. By mechanical and lytic action the eggs escape from the vessels, pass through the tissues and escape into the lumen of the intestine, together with blood and mucus and, later in the infection, with cellular débris. On evacuation in the feces these eggs are fully developed. Those of *S. japonicum* are broadly ovoidal and straw colored and measure 70 to 100 by 50 to 65 microns; those of *S. mansoni* are elongated ovoidal, have a prominent lateral spine near one end and measure 114 to 175 by 45 to 68 microns.

When the stools containing these eggs (Fig. 136) are diluted with fresh water, the eggs soon hatch, and a ciliated larva (*miracidium*) is set free from each shell, to swim about in the water. In endemic foci the miracidia attack certain species of snails in the immediate vicinity, invade the soft tissues of the snail and by a two-fold multiplication covering four weeks or more give rise to a large progeny of fork-tailed larvae (*cercariae*).

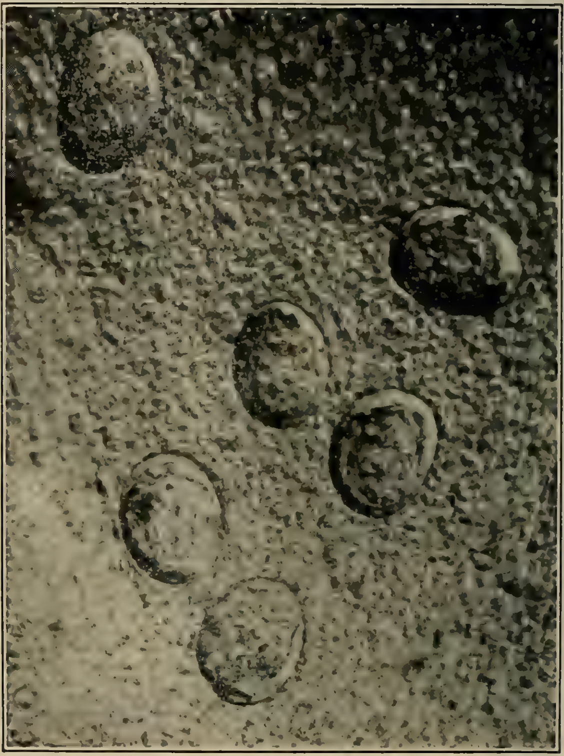

Fig. 136.—Eggs of *Schistosoma japonicum* in bloody mucous exudate from patient suffering from acute schistosomial dysentery (× 200). (From Faust's *Human Helminthology*, after Faust and Meleney, courtesy of *American Journal of Hygiene*.)

The mature cercariae escape from the snail in swarms, swim about in the water and attach themselves to the skin of persons in the water. When the water begins to evaporate, the larvae invade the skin, arrive in the peripheral venules in less than twenty-four hours and are then carried through the right chambers of the heart to the lungs. Over several days they squeeze through the pulmonary capillaries into the venules and are carried through the left chambers of the heart into the systemic circulation. Many are carried into the abdominal aorta and some into the mesenteric arteries. Only those which gain entrance to the portal circulation are able to take nourishment and develop into adults. The minimum incubation period in man, from the time of exposure to "infected water" until the adult females begin to lay eggs, is five weeks for *S. japonicum* and seven weeks for *S. mansoni.*[6]

Epidemiology.—*S. japonicum* is endemic in extensive areas in central and southern China and is found in limited foci in Japan, in Formosa, in three foci in the Philippine islands and in one locality of Celebes. *S. mansoni* occurs in many parts of Africa, in northern South America, in several of the Lesser Antilles and in Puerto Rico. Many cases of Manson's infection are observed among the Puerto Rican population in New York City. Man is the only important definitive host of the organisms. His excreta, containing the eggs, get into bodies of water in which the appropriate snails are present. Later, on direct contact with "infected water," he exposes himself to infection or reinfection. Thus, the presence and extent of the infections are conditioned by (1) the presence of the worms in the human population, (2) human habits and customs of defecation, bathing, etc., and (3) the presence of the required snail in the immediate vicinity.[6]

Pathology and Symptomatology.—Three stages are recognized: *In the first period* (five to seven weeks or more) the initial cutaneous lesions at the sites where the organisms invade the body are characterized by a nettling pruritus. Later, there is frequently an allergic reaction to foreign proteins, with giant urticaria, edema of the subcutaneous tissues and wheal formation in the skin and mucous membranes, accompanied by fever. Toward the end of this period, a toxic diarrhea develops; the liver becomes enlarged and excruciatingly tender; there is late afternoon fever, and night sweats occur.[6]

In the second period the deposition and extrusion of eggs into the intestinal wall produces a dysentery, with a microscopic picture of blood and mucus, cellular débris and the parasite's eggs in the dejecta (Fig. 136). There is daily fever, with epigastric distress and tenderness; the liver and spleen are enlarged and tender, and there is loss of weight and appetite. After a few weeks the acute attack subsides, but exacerbation occurs with exercise. At first there is a leukocytosis, with a very high eosinophilia; later a leukopenia appears, with decrease in polymorphonuclear and eosinophil leukocytes, increase in the lymphocytes and secondary anemia. Meanwhile, an increasing number of eggs have become more or less permanently lodged in the intestinal wall and in the liver by abscess and pseudotubercle reactions around them. Repair processes lead to encapsulation by fibrosis. The spleen becomes congested; its reticulum increases in amount, and splenomegaly results. The mesenteric lymph nodes lose much of their lymphoid contents. These changes are much more pronounced with *S. japonicum* than with *S. mansoni* infection, because of the much larger output of eggs and because the ovipositing worms are in greater proximity to the main portal vessels.[6]

Gradually *the third period* supersedes the second. The development of periportal fibrosis produces hepatic cirrhosis, with increased splenic congestion and, in case of profound involvement, with abdominal ascites. The mesentery and omentum become thickened, binding down the colon and producing distention of the upper and lower parts of the abdomen. The diaphragm is pushed upward, decreasing the volume of the thoracic box. The intestinal wall partakes of the fibrosis early and rapidly and loses its tonus and function. It has been likened to a hardened, worn-out rubber hose. Thus, digestion is poor; emaciation becomes pronounced, and the superficial veins of the abdomen become greatly distended. There are marked pallor, extreme dyspnea on slight exertion and profound weakness. Occasionally, carcinoma of the liver develops, or papilloma of the large bowel may become an important complication. Physical and mental development are retarded. The anemia becomes extreme. Thrombosis of the mesenteric radicles is frequent. However, the most significant abnormality in the late chronic stage is the ever-increasing portal cirrhosis. The patient may drag about for years or may die of intercurrent pneumonia or septicemia.[6]

Diagnosis and Prognosis.—No specific diagnosis can be made during the incubation period. As soon as eggs appear in the dejecta they may be classified by their characteristic appearance. In the acute stages of infection they are most common in flecks of blood and mucus passed on the outside of the fecal material. Later, when the eggs are uncommon in feces, owing to fibrosis of the bowel wall, sedimentation of the feces is advised. Prognosis is good to fair during the acute and the early chronic period, provided specific therapy is carried out. Later the prognosis is always poor, owing to extensive replacement of vital tissues in the intestine and especially in the liver.

Treatment.—*Compounds of antimony* are specifically lethal for the blood flukes. Preparation: Two types of compound are available for use, tartar emetic (antimony and potassium tartarate), sodium antimony tartrate, colloidal antimony and urea stibamine, all for intravenous administration; and fuadin (neoantimosan), for intramuscular injection. Dosage: Not to exceed a total of 1.5 to 1.8 Gm. of metallic antimony. Administration: (1) *Intravenous injection* of 60 to 100 mg. of tartar emetic or sodium antimony tartrate made up in a 2 per cent solution on alternate days or every third day for about twelve weeks; (2) *intramuscular injection* of fuadin (6 per cent solution) as follows: first day, 1.5 cubic centimeters; second day, 3.5 cubic centimeters, and on eight alternate days from the third through the seventeenth, 5 cubic centimeters each.[20] Precautions and Contraindications: Tartar emetic is contraindicated for patients with cardiac block, pneumonia, nephritis or advanced hepatic cirrhosis. Sodium antimony tartrate is somewhat better tolerated but is less stable in solution and must be made up fresh on the day of use. Care must be taken not to allow the solution to get outside the vein, or pain and sloughing of the tissues will ensue. Toxicity: Antimony introduced by vein at times produces nausea, vomiting, alveolar and bronchial irritation and rigors and is poorly tolerated by the liver.[6,11] Fuadin produces none of these objectionable sequelae. Efficiency: The preparations for intravenous use are possibly somewhat more efficient than fuadin, but the latter drug is better tolerated and is more readily administered to children.

Prevention.—Blood fluke infections can be prevented by only one certain method, namely, the sterilization of human feces or of feces used as fertilizer before they come in contact with soil or water.

Flukes Living in the Intestinal Tract, Producing Intestinal Trematodiasis.—Etiology and Biology.—This group includes the large intestinal fluke (*Fasciolopsis buski*), many species of echinostomes and many species of heterophyoid flukes, including *Heterophyes heterophyes* and *Metagonimus yokogawai.*

F. buski is a relative of the sheep liver fluke (*Fasciola hepatica*). It is a large fleshy worm, a few centimeters long, at least a centimeter wide and a few millimeters thick. It has two powerful suckers, by which it attaches itself to the wall of the duodenum and upper level of the jejunum. It lays many large, ovoidal, thin-shelled, operculate eggs (130 to 140 by 80 to 85 microns), which are immature when passed in feces, maturing in water and hatching. The emerging larvae then invade their snail hosts. After several weeks the cercarial progeny swarm out of the snail and encyst on aquatic vegetation. When man consumes the vegetation raw, he swallows the cysts, which then excyst in his duodenum, after which the emerging larvae become attached to his bowel wall and in about three months develop into adult worms.[6]

The echinostomes vary from species nearly as large as *Fasciolopsis* to forms only a few millimeters in length. Each is commonly provided with a cervical collar of spines. They are attached to the upper part of the intestinal wall by their suckers. Some species lay large and others medium-sized or small eggs, all of which are operculate, ovoidal and immature when passed in feces. After maturing and hatching, the larvae invade appropriate snails and produce cercarial progeny, which swarm out and encyst on aquatic vegetation, in the flesh of fishes or in the soft parts of the same or other species of snails. Man acquires infection from eating raw the vegetable or animal tissues containing the cysts.[6]

The heterophyid flukes are usually smaller than a mustard seed. They live in the glandular crypts or at times within the mucosa of the upper levels of the small bowel. Their eggs are about 28 by 16 microns, thick shelled and operculate and are fully developed when passed in feces. They require ingestion by their snail hosts before they hatch. The cercarial progeny which emerge from the snails invade the tissues of fishes, and these, consumed when inadequately heated, are the vehicle of infection in man.[6]

Epidemiology.—These several species of intestinal flukes are prevalent in many countries, but particularly in the Far East. For many species there are important reservoir hosts. Thus, man is not primarily responsible for their propagation, but acquires infection from consuming raw the animal or vegetable tissues containing the encysted larvae.

Pathology and Symptomatology.—The symptoms vary greatly, depending on the size and number of the worms. The larger flukes traumatize and ulcerate the wall of the upper levels of the small intestine, allowing pathogens to enter the open lesions. Their by-products are absorbed into the system and produce profound intoxication. In typical moderate infection with *Fasciolopsis* there are a debilitating diarrhea, much undigested food being passed in the dejecta; acute epigastric pains, which are caused by ingestion of food, and edema, especially of the face, abdomen and lower extremities (Fig. 137). Later, abdominal ascites, anorexia, nausea and vomiting appear; the skin becomes harsh and dry, and prostration is extreme. Usually there are pronounced eosinophilia and erythropenia.

Studies in the Philippines have demonstrated the presence of heterophyoid eggs in the bloodvessels and infiltrated in the tissues of the heart, brain and spinal cord. In the cases of heart lesions the diagnosis had been beriberi, while lesions in the central nervous system had produced symptoms of embolism.

Treatment.—1. *Caprokol* (*hexylresorcinol crystoids*), as administered for ascariasis (*vide supra*, p. 604), is probably the therapeutic agent of choice.[24]

Post-treatment saline purgation is needed to remove the dying worms. 2. *Carbon tetrachloride,* as administered for hookworm disease (*vide supra,* p. 607), is very efficient, but is not as safe as caprokol. Post-treatment saline purgation is indicated. 3. *Tetrachlorethylene,* as administered for hookworm disease (*vide supra,* p. 607), is used.[6,11]

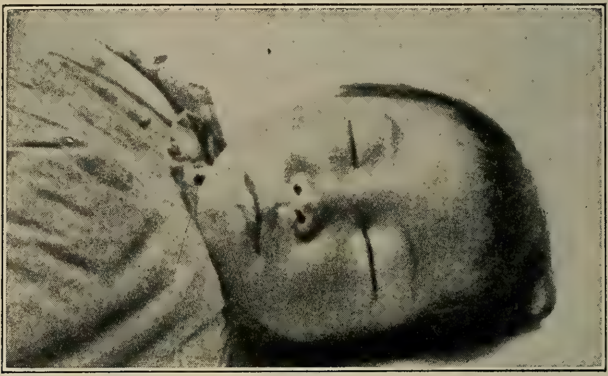

Fig. 137.—Clinical infection with the large intestinal fluke (*Fasciolopsis buski*), showing edema of the face, especially around the eyes. (From Faust's *Human Helminthology,* photo by Dr. C. H. Barlow.)

Prevention.—Since many of these worms are maintained in reservoir hosts, only one control measure will be effective in preventing infection in man, namely, the thorough cooking of all food consumed in endemic foci.

Liver Flukes, Producing Hepatic Trematodiasis.—Etiology and Biology.—This group includes the sheep liver fluke (*Fasciola hepatica*), the sheep lancet fluke (*Dicrocoelium dendriticum*), the Chinese liver fluke (*Clonorchis sinensis*), *Opisthorchis felineus,* etc. As adults, these worms live in the bile passages of their hosts.

F. hepatica is a relatively large and fleshy fluke, measuring 2 or 3 centimeters by 0.5 to 1.2 centimeters. It lives in the proximal bile ducts and lays large, ovoidal, thin-shelled, operculate eggs which are not readily distinguished from those of *Fasciolopsis buski* (*vide supra,* p. 624). These eggs pass out of the bile ducts into the intestinal tract and are evacuated in the feces. After developing in water, the eggs hatch, and the escaping larvae invade their appropriate snail hosts. The cercarial progeny which swarm out of the snail become encysted on vegetation. Consumption of the vegetation provides the route for infection of the definitive host. The larvae escape from the cysts in man's duodenum or jejunum, bore through the intestinal wall and migrate *via* the peritoneal cavity or portal vessels to the liver. They then bore through the liver parenchyma to the proximal bile ducts and grow into adult worms.

D. dendriticum is a much smaller, elongated ovoidal, flattened worm. Its eggs are considerably smaller than those of *F. hepatica,* have a thicker, golden brown shell with a conspicuous operculum and are immature when passed in feces. The phase of the life cycle outside the definitive host in general resembles that of *Fasciola.* Infection results from ingestion of vegetation to which masses of cysts have become attached. The excysted larvae in the duodenum migrate directly through the ampulla of Vater up to the bile ducts, where they develop into adult worms.

C. sinensis and *O. felineus* are delicate, transparent, lanceolate worms, typically living in the distal bile passages. Their eggs (Fig. 138, *10*) are

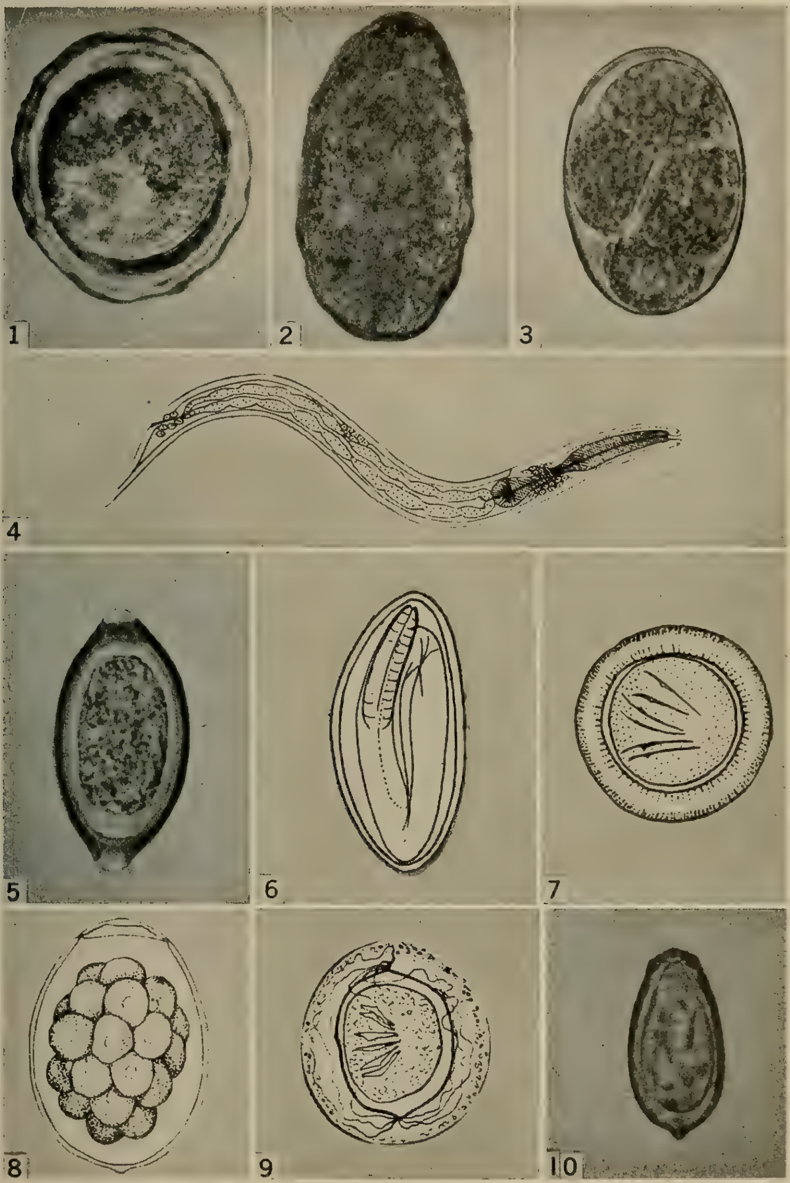

Fig. 138.—The more common helminth eggs and larvae recovered from human feces: *1*, fertilized, and *2*, unfertilized eggs of *Ascaris lumbricoides* (×600); *3*, hookworm eggs in stage frequently passed in feces (×666); *4*, rhabditiform larva of *Strongyloides stercoralis* (×310); *5*, egg of *Trichocephalus trichiurus* (×666); *6*, egg of *Enterobius vermicularis*, fully embryonated (×666); *7*, egg of *Taenia solium* (×666); *8*, egg of *Diphyllobothrium latum* (×500); *9*, egg of *Hymenolepis nana* (×466); *10*, egg of *Clonorchis sinensis* (×830). (Figure 138, *6*, is original; all other illustrations are from Craig and Faust's *Clinical Parasitology*.)

very small, thick shelled and conspicuously operculate and contain fully mature larvae when passed in the feces. They must be ingested by their appropriate snail hosts before they hatch. The cercarial progeny which swarm out of the snails encyst in the flesh of fresh water fishes. When the definitive host eats inadequately cooked fish in endemic areas, he is exposed to infection. Excystation occurs in the duodenum, and the escaping larvae migrate up through the ampulla of Vater to the distal bile passages, where they develop into adult worms.

Epidemiology.—*F. hepatica and D. dendriticum* are cosmopolitan in their distribution, but are confined principally to sheep-raising areas. Sheep are their most important definitive hosts. *C. sinensis* is prevalent in extensive areas throughout the Far East, and *O. felineus* in eastern Europe, the U.S.S.R. and parts of the Orient. Man, dogs and cats are the principal hosts. *Fasciola* and *Dicrocoelium* infections are contracted from eating vegetation to which the encysted larvae are attached; *Clonorchis* and *Opisthorchis* infections result from eating raw fish.

Pathology and Symptomatology.—*F. hepatica* produces extensive damage to the parenchyma of the liver during its larval migration to the bile passages. The adult worms of all species of liver fluke provoke a hyperplasia of the lining of the bile passages, an enveloping fibrosis of the ducts, a pressure necrosis of the substance of the liver and periportal cirrhosis of the organ. The damage is more rapidly produced by *Fasciola* than by the other worms, because of its greater size. However, in clonorchiasis and opisthorchiasis there is more likelihood of a continuous reinfection over a period of years, with a painful enlargement of the liver, passive congestion of the spleen, icterus, cholecystitis with colic, cholangitis, toxic edema and ascites. At times the pancreas is invaded by the worms, and more acute digestive and systemic manifestations occur. The toxic manifestations include palpitation of the heart and tachycardia, vertigo, tremors, tetanic cramps and mental confusion. There may be a hyperplasia of the bone marrow. Moderate eosinophilia is frequent.

Diagnosis and Prognosis.—Diagnosis is based on the recovery of the specific eggs in the feces. *Fasciola* eggs require differentiation from those of *Fasciolopsis*. When the two infections are coextensive, biliary drainage provides a helpful method for obtaining *Fasciola* eggs. Similarly, *Clonorchis* (Fig. 138, *10*) and *Opisthorchis* eggs must be distinguished from those of the heterophyoid flukes (*vide supra*, p. 625). Prognosis is good to fair for light infections, but becomes poorer as the infection becomes heavy by repeated reinfection or as a result of the pressure atrophy of the liver parenchyma.

Treatment.—*Fasciola* infection is not amenable to treatment until the maturing worms arrive in the bile passages. The most satisfactory chemotherapeutic agent for this infection is *emetine hydrochloride*, administered intramuscularly, one-half grain (0.03 Gm.) daily, for seventeen to eighteen days.[21] *Clonorchis* infection in its early stage yields to *gentian violet* treatment.[14] The one and a half hour or two hour Seal-Ins or Enseals coated tablets are administered 1 grain (0.06 Gm.) three times daily before meals for sixteen days. For chronic infections, when the bile passages have become walled off by fibrous encapsulation, the results are less satisfactory. There is no known specific treatment for *Dicrocoelium* or *Opisthorchis*.

Prevention.—For *Fasciola* and *Dicrocoelium* infections control primarily requires the elimination of the parasites in the sheep-raising areas. For

Clonorchis and *Opisthorchis* infections the thorough cooking of fish will protect the human population.

INTESTINAL MYIASIS

Etiology and Biology.—Myiasis is the invasion of the animal body by maggots, which are the larvae of flies. It may be specific, semispecific or accidental. It is usually designated according to the tissues of the body invaded, as cutaneous, ophthalmic, aural, rhinopharyngeal, intestinal, urethral, etc. In the great majority of human beings clinical myiasis affects the skin and subcutaneous tissues, but accidental infestation of the intestine is not infrequent. The gravid mother fly oviposits or larviposits on human food, which is then ingested. The eggs or larvae survive passage through the stomach and may remain temporarily attached to the bowel wall for weeks or months. However, the maggots cannot remain in the intestine indefinitely, since they must pupate on the ground. Furthermore, no multiplication occurs in the intestine.

Epidemiology.—Wherever filth flies, including the common house fly, the lesser house fly, the nonbiting stable fly, the blue bottle, the green bottle, the blow fly, the flesh fly, etc., breed in abundance, accidental myiasis may be anticipated. Infestation results from the ingestion of eggs or larvae of the fly laid on human food.[6]

Pathology and Symptomatology.—Temporary irritation of the bowel wall results in indigestion and diarrhea, with occasional dysentery. The migration of the maggots out of the anus at times produces a pruritus which may be mistaken for that occurring in oxyuriasis. In small children, reflex nervous symptoms, such as nausea and vomiting, insomnia, loss of appetite and even convulsions, may result.[6]

Diagnosis and Prognosis.—Diagnosis is based on the recovery of maggots migrating out of the anus or passed in the feces. However, great care must be exercised to prevent contamination of the feces after defecation has occurred. The prognosis is always good.

Treatment.—Saline purgation, particularly with Glauber salts ($\frac{1}{2}$ ounce, or 15 Gm., dissolved in a glass of water), to dissolve the mucus adhering to the intestinal wall, is helpful in evacuating the maggots. If specific therapeusis is desired, the administration of *caprokol* (*hexylresorcinol crystoids*), as prescribed for ascariasis (*vide supra*, p. 604), is recommended.

Prevention.—Protection can be provided only by the reduction in fly breeding in towns and on the farm. Garbage should be kept in closed containers, collected daily and disposed of by complete incineration. Outdoor toilets should be screened, and stable manure should be placed on racks over concrete drainage pits connected with septic tanks or drains. Screening of homes, especially of the kitchen and dining room, is an essential part of the control program.

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CHAPTER XXIX

BACILLARY DYSENTERY

PRESENT DAY INCIDENCE OF BACILLARY DYSENTERY

Recent clinical reports indicate the wide prevalence of bacillary dysentery in new and atypical forms. With more frequent recognition of the disease there has also occurred a better understanding of many obscure forms of acute and chronic intestinal infection. Careful epidemiologic, laboratory and clinical studies reveal that in a surprisingly high proportion of cases so-called colitis, enteritis and enterocolitis are bacillary dysentery

Reported Incidence of the Dysenteries and Typhoid-Paratyphoid in the United States, 1933–1941

	1933	1934	1935	1936	1937	1938	1939	1940	1941
Unclassified dysentery	17,043	8,189	4,961	5,824	4,940	674	1,183	1,484	1,553
Bacillary dysentery	625	2,197	7,241	11,555	10,428	20,644	21,327	19,152	24,427
Amebic dysentery	1,573	1,994	1,388	1,483	1,674	2,538	3,039	2,991	3,180
Typhoid-paratyphoid	23,349	22,217	18,355	15,898	16,033	14,903	13,069	9,809	8,539

Note the steady rise in the number of cases of *bacillary dysentery*, the incidence in 1941 being forty times that in 1933. There is a coincident inverse relation of *bacillary* to *unclassified dysentery*.

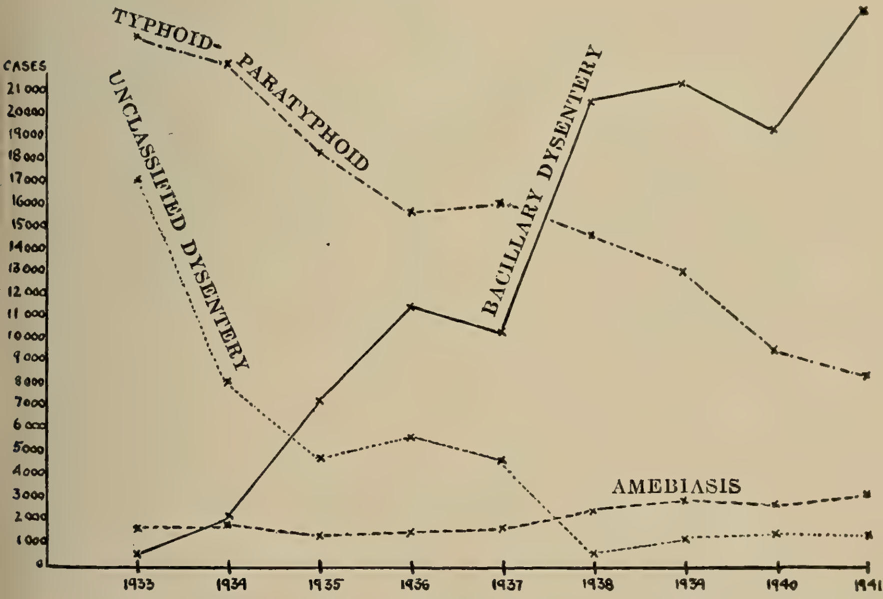
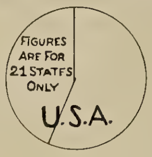


Fig. 139.—Chart showing incidence of bacillary, amebic and unclassified dysentery from 1933 to 1941.

The frequency with which these cases occur in the United States was indicated by my direct inquiries of public health officers.[13] One of the greatest difficulties encountered was the rather loose use of the terms "enteritis" and "dysentery." It was found necessary to exclude all cases except those of unquestioned bacillary dysentery, even though the broader classification included many cases of this disease. This point is illustrated by a comparative study of the United States Public Health reports for the years

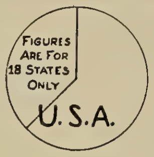
1933 to 1941. By consolidating the monthly reports it was found that *as the reported cases of bacillary dysentery increased, the incidence of unclassified dysentery fell.* Moreover, the reported incidence of bacillary dysentery in 1941 was forty times that in 1933. Personal communications from state health officers indicated that the reported cases of "diarrhea, enteritis and dysentery" in the United States from 1933 to 1937, inclusive, were 79,042 for 21 states, with a yearly average of 15,808 and a ratio of reported cases to reported deaths, for all ages, of 17.8 per cent. In 18 states during the same period there were 56,102 cases of bacillary dysentery reported, with a yearly average of 11,220+ and a case fatality for 6 states of 15.7 per cent. These figures indicate the wide prevalence of diarrheal diseases in general and of bacillary dysentery in particular. They suggest the importance of intensive effort to clarify the status of the disease, which is readily admitted by many public officials to be extremely unsatisfactory and fraught with danger. It has also been conceded by some investigators that bacillary dysentery already far exceeds typhoid fever as a public health problem in the United States. In Virginia, where the incidence of bacillary dysentery is extremely high during the summer, McGinnes and his co-workers[25]

THE DYSENTERY PROBLEM, BASED ON PERSONAL COMMUNICATIONS FROM STATE HEALTH OFFICERS. INCIDENCE OF DIARRHEA, ENTERITIS AND DYSENTERY IN THE UNITED STATES, 1933–1937



Total cases	79,042
Yearly average	15,808
Average mortality for 6 states	17.8%

INCIDENCE OF BACILLARY DYSENTERY IN THE UNITED STATES, 1933–1937



Total cases	56,102+
Yearly average	11,220+
Average mortality for 6 states	15.7%

The increasing number of outbreaks of *bacillary dysentery* in New York State 1932–1937. Note tendency to reversal of Flexner: Sonne-Duval ratio.

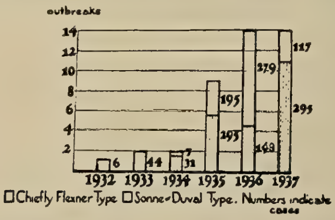


FIG. 140.—Chart showing incidence of diarrhea, enteritis and dysentery in the United States from 1933 to 1937.

reported a winter incidence of 13 per cent of bacteriologically positive disease in October. "Of 688 apparently well persons in household contact with studied cases of dysentery and diarrhea 17.6 per cent were found to be carriers of B. dysenteriae." In New Mexico, Hardy [21] found that in two small isolated villages where clinical diarrhea was endemic, more than 10 per cent of the population harbored *Bacillus dysenteriae.*

TYPICAL AND ATYPICAL CLINICAL FORMS OF ACUTE BACILLARY DYSENTERY

Typical acute bacillary dysentery is readily diagnosed. The average incubation period in the New York area is somewhere between twenty-four and thirty-six hours. The symptoms are described in the section on diagnosis. It is difficult to make any dogmatic division into clinical types based on the degree of severity of the disease. Generally speaking, the Shiga-Kruse type is more severe than Flexner dysentery and the attendant mortality correspondingly higher. That this is not always true, however, is attested by the sudden deaths which occasionally occur from rather mild Sonne-Duval dysentery. Moreover, the latter type is often as severe as the Shiga-Kruse type.

The atypical forms of acute bacillary dysentery are not so readily diagnosed and account in part for the widespread dissemination of the disease. Huntington[23] traced the influence of climate on civilization, necessitating mass migrations and adaptions to new lands. With these changes there have occurred certain disease adaptations, well exemplified by bacillary dysentery. Originally a disease of tropical or semitropical regions and primitive peoples, it has come down through the ages in many new and hitherto unrecognized forms. Improved methods of travel, crowding of cities and ineffective public health control have favored wide dissemination of the disease in spite of the presumed high standards of hygiene and sanitation among civilized peoples. The North Temperate Zone and even the Artic regions have provided virgin fields for a disease which has adapted itself to a changed environment and climate. These adaptations have been signalized by the appearance of the following new clinical types:

1. **Sonne-Duval Type.**—Although originally described by Duval and Shorrer[3] in 1904, this type of dysentery was given its chief impetus to clinical interest by Sonne[28] in 1915. Since then, reports have appeared from France, Denmark, Norway, Sweden, Japan, Scotland, England, Australia, South Africa, Canada and the United States. Owing either to better recognition of the disease or to an actual rising incidence, there has been a steady increase in the number of outbreaks and of individual cases in New York State (Table 22), particularly interesting since in New York, as in England, Scotland and Denmark, the prevalent tendency in recent years has been toward a reversal of the usual Flexner to Sonne-Duval ratio, the latter type equaling or predominating over the former.[1] While the majority of patients are children under ten years of age, my experience with this type of dysentery since 1933 has shown an increasing prevalence among adults. The disease falls into three clinical groups: symptomless, mild and severe.[15] In the symptomless type, the diagnosis is usually made in the course of an epidemiologic survey. No history of any noteworthy

indisposition, fever or diarrhea may be obtained, but cultures of the feces and of material obtained by sigmoidoscopic crypt aspiration are positive, and a moderate degree of mucosal hyperemia and punctate follicular hyperplasia are present. There is a rising agglutination titer, often not higher than 1:60. All laboratory and clinical signs usually disappear within seven to ten days. The mild type is probably the most frequent. The distinguishing clinical features are a shorter duration and a lessened tendency to pyrexia, tenesmus and bloody bowel movements in comparison with the other forms of acute bacillary dysentery. The onset is generally marked by only a slight lassitude or anorexia. There is a mild diarrhea with mucus; the stools are soft and greenish or watery and specked with bright red blood, and the number of movements varies from three to eight in twenty-four hours. The surprising feature is the comparative well-being of the patient, who complains little or not at all. After a period varying from a few days to perhaps two weeks, the bowel movements gradually diminish; the feces become well formed, and the disease appears to be at an end. There are generally no bad after-effects and no noteworthy prostration, anorexia or loss in weight. The symptomless and mild forms are nearly always responsible for institutional outbreaks of Sonne-Duval dysentery, because the disease is not recognized. My associates and I traced one such outbreak to a patient who had been admitted to the hospital with symptoms misinterpreted as those of acute appendicitis. On the day of admission and during the entire postoperative period there were many bowel movements, averaging seven daily, and the stools contained bright red blood. At the time of our investigation the patient had been discharged from the hospital for eight weeks. We succeeded in obtaining positive cultures, however, from the patient and two other members of the family who had been suffering from "colitis" for approximately two months. Interval contact subjects were easily traced thus definitely linking the outbreak with the initial patient discharged eight weeks before.

TABLE 22.—OUTBREAKS OF SONNE-DUVAL DYSENTERY IN NEW YORK STATE[20]

	Outbreaks	Cases
1932	0	0
1933	0	0
1934	1	31
1935	5	295
1936	5	148
1937	9	295

With the increasing incidence of Sonne-Duval dysentery, there has appeared a severe form of the disease, affecting both children and adults. In one instance in which the exact hour of contact could be definitely ascertained the incubation period was twelve hours. Further experience demonstrated that in the New York area the average incubation period for all types of bacillary dysentery was somewhere between twenty-four and thirty-six hours. The severe type is ushered in by rather sudden abdominal camps and frequent watery stools containing mucus and bright red blood. Vomiting may be severe and is accompanied by profound prostration. The temperature may remain as high as 104 or 105 F. for several days and then gradually subside to normal, with cessation of the diarrhea and improvement of subjective symptoms by the seventh to the tenth day. The sudden onset in these cases often leads to the erroneous diagnosis of "food poisoning." It is the rule in this as in other types of acute bacillary dysentery that subsidence of symptoms is not coincident with complete healing of the ulcerated bowel. Repeated sigmoidoscopic examinations generally reveal that the most rapid healing occurs during the postdiarrheal period of constipation.

2. **Appendicular Type.**[3]—This type is well defined, with colicky abdominal pain localized to the right lower quadrant, vomiting and the temperature elevated to 101 or 102 F. Anorexia, lassitude and headache may occur in the prodromal period, but are less likely with the Sonne-Duval than with the Flexner infection. Tenderness is generally present at McBurney's point, particularly on rebound, and shifts with changes in position of the body. A spastic ileum and sigmoid flexure may be felt, and constitute an important diagnostic feature because intestinal spasm occurs early in dysentery and persists for some time. In thin persons, enlarged mesenteric or epicolic lymph nodes may be felt near the ileocecal angle.

DIFFERENTIAL DIAGNOSIS

Appendicular Form of Bacillary Dysentery	*Acute Suppurative Appendicitis*
1. History of "food poisoning".	1. Sudden onset, often without history of dietary indiscretion.
2. History of diarrhea or contact with a person who has had diarrhea.	2. Diarrhea unusual; no history of contact.
3. Moderate initial pyrexia.	3. High initial pyrexia.
4. Lax abdominal wall.	4. Muscular rigidity.
5. Spastic ileum or sigmoid flexure.	5. No spasm of ileum or sigmoid flexure.
6. Enlarged mesenteric nodes felt at the ileocecal angle in thin persons.	6. Mesenteric nodes usually not felt.
7. Patient appearing well and relatively comfortable.	7. Patient acutely ill.
8. Absence of leukocytosis; leukopenia frequent.	8. Leukocytosis with increase in band forms.
9. Positive culture obtained from the feces early in the disease.	9. Culture obtained from the feces negative for *B. dysenteriae.*
10. Agglutination titer present late in the disease.	10. No agglutination of *B. dysenteriae,* except in some patients who have recently recovered from the disease.
11. Diagnostic bacteriophage present.	11. No diagnostic bacteriophage, except in circumstances specified in item 10.
12. Appendix grossly appearing normal.	12. Appendix acutely inflamed.
13. Mesenteric adenitis.	13. Mesenteric adenitis rarely as pronounced as in bacillary dysentery.
14. Appendicular lymphoid hyperplasia with focal necroses of the solitary lymph nodules.	14. Appendicular necrosis with suppuration or gangrene.
15. Inflammation of the distal portion of the ileum in some cases.	15. No inflammation of the distal portion of the ileum.
16. Hyperplasia of Peyer's patches and solitary acuminate lymph nodules in the appendix, ileum and colon.	16. Ileum and colon not involved; intramural acute suppurative inflammation of all the coats of the appendix.
17. Appendicular symptoms usually clear within twenty-four hours or less, but diarrhea of increasing severity persists.	17. Appendicular symptoms persist.
18. Removal of appendix unnecessary.	18. Removal of appendix imperative.

A history of diarrhea is helpful in reaching a diagnosis, particularly if mucus and bright red blood have been present. When the right lower quadrant symptoms occur at the onset of the disease, diarrhea may not be evident until the following day. In some cases appendicular symptoms occur on or after the sixth day, when diarrhea is no longer a prominent feature. The leukocyte count may be almost normal, or there may be actual leukopenia. When the diagnosis of bacillary dysentery has been overlooked or is in doubt, the patient is promptly operated on. The usual findings are a normal-appearing appendix but a rather mystifying mesenteric lymphadenitis. The regional mesentery is often studded with enlarged pinkish nodes. There is also apt to be an acute distal ileitis, in which the terminal portion of the ileum at or near its junction with the colon exhibits a segmental, clearly demarcated zone of inflammation, varying in extent 3 to 30 centimeters. The affected bowel wall is reddened, enlarged, thickened and succulent, and the mesenteric vascular arborizations stand out prominently. If this picture is noted, the best procedure is to close up the abdomen immediately. Any attempt to resect the ileum is apt to be followed by peritonitis and death, since the intramural infection often extends beyond the line of demarcation visible to the naked eye; nor is the zonal area of lymphadenitis any more reliable a criterion. Appendectomy is often followed by a persistent fecal fistula.

3. **Meningitic Type.**—This type was present in 13 per cent of the hospitalized patients in the Jersey City epidemic of Flexner dysentery of 1934.[19] The patients in this group exhibited rigidity of the neck and positive Kernig and Brudzinski signs. The chief symptoms were severe headache, violent emesis, convulsions and drowsiness or stupor. Spinal tap, however, revealed a clear fluid with a normal cytologic picture and the presence of sugar; there was no globulin, and culture was negative. This clearly defined group was apparently infected with a neurotropic Flexner strain, which produced the thermolabile exotoxin described by Olitsky and Kligler[26] for *B. dysenteriae* (Shiga). An interesting feature in all cases of meningitis was the presence of a nasal or labial herpes, which persisted for seven to ten days and occurred only in this group. My associates and I postulated the rather constant association of a virus with this neurotropic strain of Flexner organism. The clinical signs and symptoms of meningitis gradually disappeared in twenty-four to seventy-two hours, to be succeeded by the typical intestinal manifestations of dysentery.

4. **Agranulocytoid Type.**[6]—In Sonne-Duval infections leukocyte counts of 4,000 cells per cubic millimeter are frequent. I have seen several patients with acute fulminating bacillary dysentery who exhibited a progressive toxic neutropenia with fatal termination within five weeks. The total leukocyte count fell below 1,000 cells, the granulocytes ranging from 2 to 10 per cent and exhibiting varying degrees of toxic change, such as swelling of the cell bodies, coarse irregular cytoplasmic granulation with vacuolation and focal pyknotic areas in the nucleus with partial or complete disintegration. Two of the patients came to necropsy, and bone marrow sections showed no evidence of deficiency in granulocyte production. The marked toxic granulocytopenia was therefore due either to the destructive action of the toxin on the cells of the peripheral blood or to a necrotizing effect on the vascular sinusoids of the bone marrow, into which the granulocytes must migrate from their extravascular zone of production.

The chief clinical feature of this type of bacillary dysentery is severe diarrhea with blood and mucus, accompanied by tenesmus, abdominal pain and marked prostration. The patient appears to be overwhelmed by a profound toxemia; the features portray anxiety, with pinched facies and flushed, hollowed cheeks and temples. The major symptoms are present in the abdomen, which is greatly distended and diffusely tender. The pulse is rapid and the skin dry, and there is evidence of generalized dehydration. Anorexia is marked, but the mentality is keen. Sigmoidoscopy reveals multiple discrete and confluent serpiginous and geographic denudations of the mucosa, with free bleeding and mucopus. The temperature remains constant between 102 and 103 F. The Sonne-Duval, Flexner and Mount Desert organisms were the causative agents in the cases studied, furnishing further evidence of the protean character of bacillary dysentery and direct contradiction of the widespread belief that Sonne-Duval dysentery is a mild and rather innocuous type of infection.

5. **Pneumonic Type.**[10]—The association of upper respiratory tract symptoms with mesenteric lymphadenitis in acute bacillary dysentery has been noted chiefly in children with the Sonne-Duval type of infection. Thus far the pneumonic type of bacillary dysentery has been noted only in adults infected by the Flexner organism. There is a prodromal period of twenty-four to forty-eight hours, during which the chief complaints are suggestive of "grippe," *viz.*, malaise, headache, anorexia, nausea and indefinite muscle pains or "body aches." This is followed by a chill and a sharp rise in temperature, which may reach 105 or 106 F. There are marked prostration, a rapid pulse and a short nonproductive cough. The cheeks are flushed, and on ausculation of the chest fine moist rales are heard, which persist after coughing. The entire picture is suggestive of lobar pneumonia, and a roentgenogram taken in one instance at an early stage revealed a localized area of increased density, measuring approximately 10 centimeters in diameter, in one lung. This was interpreted by the roentgenologist as beginning pneumonic consolidation. Within approximately twenty-four hours the entire clinical picture changes, and with it there is gradual and complete subsidence of ausculatory and roentgenologic signs in the chest. The patient complains of abdominal cramps accompanied by frequent blood-tinged and mucoid stools, which may mount to twenty to thirty per day. There is marked tenesmus, and often the stool consists entirely of blood-flecked mucus. With the onset of diarrhea, which favors the elimination of the toxin, the temperature usually recedes somewhat. The intestinal lesions progress through the characteristic stages, which will be noted in the section on pathology, the general clinical features corresponding to those of a typical, moderately severe bacillary dysentery.

6, 7, 8. **Asymptomatic, Afebrile and Constipation Types.**—These three types will be considered together, since they are almost impossible to diagnose except in the course of epidemiologic surveys. The interesting feature of these rather paradoxic forms of dysentery is that the patients affected are not healthy carriers. Repeated sigmoidoscopic examinations generally reveal the characteristic first and second stages of bacillary dysentery (*i. e.*, punctate follicular hyperplasia and punctate follicular necrosis). The disease runs a mild course with a moderate rise in agglutination titer and a transient fecal culture for *B. dysenteriae*. Patients with these types are frequently responsible for spread of the disease, an observation which makes it imperative that *with bacillary dysentery every contact be examined and cultures made for evidence of infection*. No suspect should be released from isolation until fresh fecal cultures on three successive days give negative results.

THE DIAGNOSIS OF ACUTE BACILLARY DYSENTERY

Aside from recognition of the important new forms of the disease, diagnosis of typical acute bacillary dysentery will rest on the following clinical and laboratory features:

1. **General Clinical Symptoms and Signs.**—A prodromal period of twelve to forty-eight hours of malaise, headache, anorexia and nausea, accompanied by a moderate elevation of temperature, is followed by abdominal cramps and profuse watery diarrhea. The fever increases; cramps, diarrhea and tenesmus become more marked, and mucus, mucopus or bright red blood appears in the stool. A tender, spastic ileum and sigmoid flexure may be felt through a thin or relaxed abdominal wall. Sigmoidoscopy reveals an intense acute inflammation of the intestinal mucosa, which is glistening, edematous and covered with mucus and appears to be "weeping" blood. During the first twenty-four hours punctate follicular hyperplasia is present, the enlarged solitary acuminate lymph nodules standing out prominently like discrete grains of sand on a reddened background. Often a twig of engorged small mesenteric vessels will be seen embracing individual follicles. This is readily visualized through the sigmoidoscope by the naked eye or with the aid of a green filter[11] and a telescopic device. After the initial phase of hyperplasia the centers of the lymph follicles and overlying mucosa become necrotic. This is the stage of punctate follicular necrosis, which generally occurs on the second or third day of the disease. After this time the discrete areas of necrosis and ulcer-

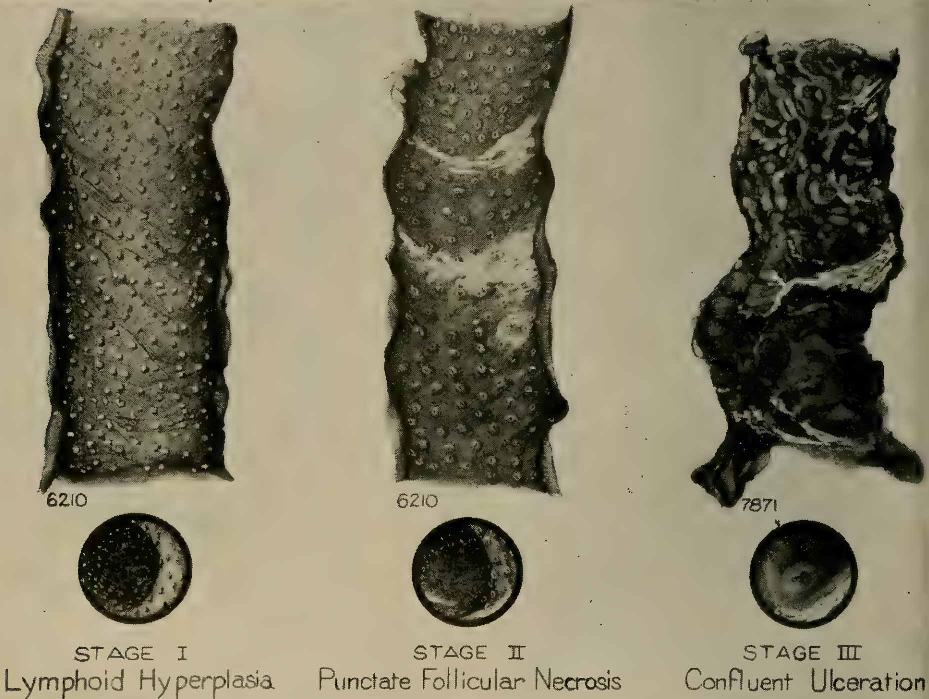


FIG. 141.—Characteristic three stages of acute bacillary dysentery.

ation tend to become confluent. If the outcome is favorable, further progress of the disease is arrested between the seventh and the tenth day, at which time the diarrhea and cramps abate and constitutional symptoms improve. A rather obstinate constipation ensues, a phenomenon which probably represents nature's effort to splint the bowel to favor healing. In a small proportion of cases deep intramural infection occurs, and eventually perforation. All the developmental phases have been followed in the living patient by sigmoidoscopy. This procedure is innocuous in skilled hands and is an invaluable adjunct to clinical diagnosis. No other disease even remotely resembles acute bacillary dysentery in its progressive pathologic manifestations. In amebiasis the incubation period is generally much longer and the onset less acute. The ulcers are discrete, have undermined edges and are surrounded by hemorrhagic halos. The intervening mucosa is not acutely inflamed, and crypt aspiration smears lack the specific cytologic features of bacillary dysentery. It must be borne in mind, however, that double infections with *B. dysenteriae* and *Endamoeba histolytica* or *Bacillus typhosus* sometimes occur.

2. **Laboratory Criteria.**—Leukopenia is often present at the onset of the disease and may continue throughout. The diagnostic tetrad consists of a positive culture early in the disease, a rising agglutination titer and bacteriophage at a later period and a purulent exudate. Cytologic study of the latter reveals many polymorphonuclear leukocytes, some of which are undergoing toxic degeneration, as well as erythrocytes and large mononuclear cells or macrophages. More strongly positive cultures are obtained by the mucosal crypt aspiration-spray culture method[12] than by examination of fecal specimens.

PATHOGENESIS OF ACUTE BACILLARY DYSENTERY[7]

Acute bacillary dysentery may be defined as a systemic disease due to *B. dysenteriae* in which the pathologic lesions are due to one or more toxins. According to this concept the intestine, often regarded as bearing the entire brunt of the disease, is really but one of several organs that may be affected. Evidence has been presented that at times the extraenteric manifestations may be far more detrimental and may even dominate the clinical picture.

The earliest intestinal lesion that I have noted in acute bacillary dysentery is a diffuse hyperemia of the mucosa of the small and large intestines, with moderate edema and diffuse lymphoid hyperplasia of the solitary accuminate lymph nodules. The latter stand out prominently against a reddened background as grayish, punctate rounded elevations. Peyer's patches are similarly involved, a tuft of dilated bloodvessels often surrounding and penetrating the outer margins. Sections taken at this stage reveal lymphoid hyperplasia, edema of the mucosa and submucosa and some polymorphonuclear and plasma cell infiltration, with marked congestion of all the superficial vessels. The goblet cells of the mucosa are actively secreting large amounts of mucus, a process that appears to be due to irritation and furnishes a protective film to the mucosa. The picture just described corresponds to the first stage, or the stage of punctate follicular hyperplasia. On the second or third day after the onset of the disease the acute inflammation of the mucosa is intense, fresh blood appearing to ooze through relatively intact epithelium. Central punctate follicular necrosis with ulceration of the overlying epithelium occurs, the follicles appearing like the mouths of tiny diverticula. This is the second stage, the stage of punctate follicular necrosis. The punctate areas of necrosis become confluent, and rather free bleeding occurs, owing to the necrotizing action of the dysentery toxin on the walls of the submucosal vessels during the process of excretion from the blood stream through the wall of the bowel into the lumen. This is the third stage, the stage of discrete and confluent ulceration. Sections taken on the fifth to the seventh day show a marked cellular reaction in and about the floor of the ulcer, which is usually formed by the submucosa. The cellular infiltration, which consists chiefly of polymorphonuclear leukocytes, forms a rather dense line of demarcation near the ulcer, but not infrequently permeates the deeper recesses of the intestinal wall. The contiguous thin-walled bloodvessels are congested and often may be seen releasing their contents through the necrotic portions of their walls. This usually occurs in close proximity to the ulcer, so that the blood quickly finds its way through the floor to the interior of the bowel. Repair usually takes place *after* the subsidence of the diarrhea, *i. e.*, during the constipation phase which often accompanies convalescence. In uncomplicated disease healing usually occurs with complete restoration to normal by the end of the third week. I wish again to point out that cessation of diarrhea is *not* synchronous with the disappearance of the ulcers, the practical implication being that no patient should be released from observation until the ulcers have healed. For, as I shall point out later in speaking of *chronic* dysentery, it is through these ulcers that secondary nonspecific intramural infection occurs.

In some cases the inflammatory process is progressive, involving the deeper layers of the abdominal wall until the serosa is reached. The cellular infiltration is diffuse and is accompanied by edema, congestion and necrosis. Ultimately perforation and peritonitis occur, usually at about the fourth or the fifth week.

The lesions thus far described have been seen through the sigmoidoscope in adults and in necropsy specimens. *The colon is involved in every instance,* but the process is not necessarily limited to this portion of the bowel. Any part of the small or large intestine may be affected, but in many instances the disease appears to have a peculiar predilection for the distal part of the colon and the terminal portion of the ileum. I have seen 14 patients in whom the pathologic condition was most prominent in the right lower quadrant of the abdomen and consisted of mesenteric and mesocolic lymphadenitis associated with an acute inflammation of the distal part of the ileum. In most cases thus far studied the acute distal ileitis appeared to subside in a few weeks, but in some the condition persisted and became chronic.

In connection with the characteristic three stage pathologic picture of bacillary dysentery it is of interest to note that mild involvement often does not progress beyond stage 1 or stage 2. Babies with acute bacillary dysentery often die in these early stages, overwhelmed by toxemia, dehydration and acidosis.

BACTERIOLOGY OF ACUTE BACILLARY DYSENTERY

The classification and subdivision of the different types of *B. dysenteriae* has been the subject of extensive investigation in recent years.[29] Almost every outbreak or epidemic reveals strains differing from accepted types in their biochemical reactions or agglutinability. Aside from the acidification of mannite by the Flexner group and the late fermentation of lactose without gas production by the Sonne-Duval organism, reactions on sugar mediums have been too inconstant for use as a sole basis of division. Further, freshly isolated dysentery organisms are often inagglutinable. Sometimes repeated subcultures on liquid and solid mediums are necessary before a given strain will become agglutinable. Atypical dysentery strains are being constantly encountered, and their pathogenicity can often be established only by intraperitoneal injections into white mice or intravenous inoculations into rabbits of eighteen-hour broth cultures.

As a working basis, however, it may be stated that the dysentery organism is generally a short, nonmotile, Gram-negative bacillus; forms no spores; does not liquefy gelatin, and ferments certain carbohydrates without the formation of gas (exception, Newcastle bacillus). The simplest division is into (1) nonfermenters of mannite (Shiga), which form a homogeneous group, and (2) mannite fermenters (Flexner, Strong, Hiss-Russell Y, Sonne-Duval), which form a heterogeneous group.

Cultural Studies.—Speed and relative simplicity are essential in field work on the problem of bacillary dysentery. My routine has been to culture the fecal material on fresh Endo plates; pick off the colorless colonies at the end of twenty-four hours, and inoculate Russell's tubes with some and set up others directly against polyvalent diagnostic agglutinating serum. The latter method, if the results are positive, is of definite value. If negative, it may be that one is handling rough, inagglutinable strains. If, after over-night incubation, the Russell tubes show acid production without gas in the butt and no change in the slant, the culture is set up against the differential carbohydrate mediums. I have endeavored to simplify these (Table 23).

Table 23.—Cultural Characteristics of Strains of B. Dysenteriae

Group A	Dextrose	Mannite	Dextrin	Lactose	Sucrose	Rhamnose	Indole
Shiga	+	0	0	0	0	0	0
Schmitz*	+	0	0	0	0	+	+
Group B							
Flexner Y†	+	+	0	0	0	0	+
Hiss	+	+	+	0	0	0	+
Sonne-Duval*	+	+	+	+	0	+	0

Group A, nonfermenters of mannite.
Group B, mannite fermenters.
+ indicates acid; 0 indicates no acid.

It may be accepted as axiomatic that any Gram-negative, nonmotile rod exhibiting the cultural characteristics set out in Table 23 belongs to the dysentery group. Minor deviations from these characteristics when the cultures are obtained from patients possessing clinical and serologic features diagnostic of bacillary dysentery stamp the organisms as merely variants of this group.

* Schmitz and Sonne-Duval strains also produce acid on rhamnose. *B. dysenteriae* (Sonne-Duval) also ferments arabinose.

† Some Flexner strains ferment sucrose (Carter).

Other sugars have been used by various investigators for the identification of subgroups. In this connection the work of Bojlen[1a] might be mentioned. He used xylose and maltose to separate four groups of the Sonne-Duval organism, two of them fermenting xylose and all four fermenting maltose. The Flexner groups all fermented arabinose, half of them sorbitol and sucrose and only one maltose.

For supplementary studies at base laboratories doubtful strains should be identified by agglutination to full titer with monovalent serums.

The homogeneous antigenic structure of the Shiga-Kruse organism is striking. A specific serum prepared against a single strain will agglutinate all other Shiga-Kruse strains. The serum also contains some agglutinins against the Schmitz and Flexner bacilli. Anti-Schmitz serum likewise will agglutinate the Shiga-Kruse organism, but only to partial titer. Neither the Shiga-Kruse nor the Schmitz organism, however, can absorb the agglutinins from the opposite serum.

Murray (1918), Andrewes and Inman (1919) and Gettings (1919) demonstrated the antigenic heterogeneity of the Flexner group, V, W, X and Z antigens making up every Flexner strain, in varying preponderance. Thus, Flexner V, W and Z behave as distinct serologic types, each requiring its own antiserum for complete agglutination.

The general trend at the present time is to regard Boyd's classification as the most comprehensive: According to this, only the V, W and Z races of Andrewes and Inman are valid types, each having a type-specific antigen and a common group antigen responsible for the cross-agglutinations exhibited by the various races. Type X, by this classification, is a variant of Z, and type Y comprises the strains which have lost their type-specific antigen.

By means of careful serologic studies Boyd concluded that a more comprehensive classification of *Shigella paradysenteriae* could be effected. This concept is embodied in the following tables:

CLASSIFICATION OF SH. PARADYSENTERIAE (BOYD, 1940)

New	*Old*
B. dysenteriae Flexner I	Andrewes and Innman V
B. dysenteriae Flexner II	Andrewes and Inman W
B. dysenteriae Flexner III	Andrewes and Inman Z
B. dysenteriae Flexner IV	Type 103
B. dysenteriae Flexner V	Type P 119
B. dysenteriae Flexner VI	88-Newcastle-Manchester
B. dysenteriae Boyd I	Type 170
B. dysenteriae Boyd II	Type P 288
B. dysenteriae Boyd III	Type D 1

SUBCLASSIFICATION OF B. DYSENTERIAE FLEXNER VI (BOYD, 1940)

	Lactose	Glucose	Mannitol	Dulcitol
Type 88 (33 per cent of strains) . . .	—	A	A	—
Type 88 (66 per cent of strains) . . .	—	A	A	late A
Manchester bacillus	—	AG	AG	late AG
Newcastle bacillus	—	AG	—	late AG

Saccharose and indole gave negative results with all strains.

Boyd classified Andrewes and Inman's types V, W and Z and his own types 103, P 119 and 88 as true dysentery bacilli. The remaining six Flexner-like organisms do not possess a group antigen, although each has a type-specific antigen. P 170 is relatively common and is encountered in India. P 288 and D 1 are true dysentery bacilli but are relatively infrequent. Both are late dulcite fermenters. P 274 appears to be related to *B. alkalescens,* Aoki's type VII and certain gas-forming strains. It is of doubtful pathogenicity. D 17 and P 143 are extremely rare.

Not infrequently the technical difficulties incident to the transitory presence of the organism itself may be compensated for by the detection of its bacteriophage, which is group, rather than type, specific. *Repeated* examinations, at least six on successive days, should be made before the investigation is discontinued. Fresh fecal specimens are best suited for culture, but where circumstances render these unavailable, the stool may be mixed with an equal amount of glycerin to retard the over-growth of *Bacillus coli* or with a similar amount of 3 per cent sodium hydrate.

SEROLOGY OF ACUTE BACILLARY DYSENTERY

There is some divergence of opinion with regard to the reliability of agglutination titer as a diagnostic criterion of bacillary dysentery, in part concerned with the question of what constitutes a diagnostic level. In order to have a basis for comparison, the serums of 300 persons presenting no evidence of intestinal disease were titrated and served as controls for our[16] later studies of dysentery in the same area. Of the 300 serums, diagnostic titers were obtained in only 4.6 per cent for all types except *B. dysenteriae* (Sonne-Duval). For that type no positive reactions were obtained. Titers of 1:100 or over were regarded as diagnostic for all except the Shiga and Sonne-Duval types, for which 1:50 or over was considered positive. In this, as in subsequent studies, the set-up included eighteen hour viable broth culture, the gross test tube method, four hours' incubation at 55 C. and refrigeration overnight. Formalinized cultures were not used.

In connection with these studies three facts appear to be obvious: (1) A diagnostic agglutination titer in acute bacillary dysentery is often transitory. Most mild involvements with Flexner or Sonne-Duval bacillus fell in this group. The general permanence of titers acquired during an attack of acute dysentery will be shown in the section on chronic dysentery. (2) Weak agglutination titers are of rather frequent occurrence in acute dysentery.[22] (3) Bizarre cross-agglutination reactions may occur. This phenomenon is probably due to the antigenic heterogeneity of the Flexner group. Owing to the many variants of the Flexner organism, a sufficient number of smooth, agglutinable strains should be used in the set-up, particularly those prevalent in the area in which the studies are being conducted. A *rising* agglutination titer is more significant in acute bacillary dysentery than a single titer at or above the diagnostic level.

COMPLICATIONS

Aside from the major complication of perforation with peritonitis, there are complications due essentially to toxic absorption and secondary avitaminosis. Myocarditis, nephritis, disturbances in fluid balance, neuritis and arthritis have been described. The arthritic complications are of particular interest, since they occur in both acute and chronic forms. Although acute arthritis is often referred to as occurring chiefly with the Shiga infection, I have encountered it rather frequently with Flexner and occassionally with Sonne-Duval infection. The larger joints are commonly affected, particularly the knees and ankles. The effusion is serous, and the swelling is largely periarticular. The joint appears acutely inflamed and is painful, tender and held immobile. I have repeatedly cultured the fluid aspirated from such joints without result. It is possible that the disease is produced by a specific arthritic toxin, since minute doses of antigen recovered from autogenous dysentery strains when injected parenterally often produce severe exacerbation of joint symptoms. Renal infections with *B. dysenteriae* are rather infrequent, only 33 instances having been reported in the literature. To these may be added a recent case of an eighteen month old girl with advanced pyelonephritis. Repeated cultures of urine from the pelvis of the kidney and bladder, which showed a member of the Flexner group, became completely negative after removal of the kidney and ureter. The chief features of such complications are the marked predominance of females among patients affected and the frequent absence of a recognized intestinal infection with bacillary dysentery.

PREVENTIVE THERAPY OF ACUTE BACILLARY DYSENTERY

1. **Hygienic and Sanitary Aspects.**—"Food, fingers and flies" are the chief harbingers of the disease, for the germ always travels from the intestinal tract of the person who harbors it to the mouth of the victim who subsequently contracts the disease. It is literally a matter of "living from hand to mouth." In a country such as the United States, with its high standards of hygiene and sanitation, there is no excuse for the widespread prevalence of bacillary dysentery. There is perhaps no disease more susceptible to complete eradication. Poorly manned or inefficient health departments, political or commercial expediency and procrastination are the chief causes for the deplorable state of affairs. Hospital and institutional outbreaks are common. The methods of control of outbreaks have long been known to public health officials, but terminating an outbreak is nothing, compared to what might have been done to prevent it. There is a lack of adequate control of food handlers in restaurants, homes and travel conveyances, on both land and sea. Although much has been accomplished in the handling of the typhoid problem, it appears strange that the same measures have not resulted in a parallel diminution in bacillary dysentery. An obvious difficulty lies in the failure to diagnose the disease both clinically and bacteriologically, the complacent attitude toward diarrheal disease in general and the actual nonreportability of bacillary dysentery in some states (*e. g.*, Alabama, Wisconsin).

2. **Centralization of Responsibility.**—Centralization of responsibility is essential for the control of dysentery outbreaks. Authority should be given one medical officer, who should receive special training in diagnosing atypical and abortive forms of bacillary dysentery as well as other infectious diseases. The appointment of hospital epidemiologists is an important part of the Seven-Point Program of the Dysentery Registry for the prevention of infectious diarrheas (p. 645). The purpose of centralized control is to secure prompt and effective action *before* the disease has spread. Procrastination and half-way measures invariably end in defeat. Organization and military discipline are essential for the termination of outbreaks. Such a program avoids the ever-present tendency to "cover up" or minimize the

danger of an outbreak and the embarrassment of having an outsider step in to terminate it. This system has been in use at our hospital since 1933, when an outbreak of Sonne-Duval dysentery occurred. We have had no further difficulties, even though outbreaks are of frequent occurrence in institutions nearby and sporadic cases of acute and chronic bacillary dysentery are being constantly observed in our wards.

SEVEN-POINT PROGRAM FOR THE PREVENTION AND CONTROL OF BACILLARY DYSENTERY AND OTHER INFECTIOUS DIARRHEAS*

1. International coöperation for detecting cases at their source.
2. Certification of passengers and crew of ships as to presence or absence of infectious diarrhea at points of embarkation and before disembarkation.
3. Compulsory universal reporting by physicians of all infectious diarrheas.
4. Adequate sanitary supervision of transportation systems, summer camps, food and foodhandlers.
5. Education of the physician and layman in insolating every case of diarrhea until cultures for specific organisms prove negative.
6. Appointment of an epidemiologist to the staff of every hospital.
7. The prophylactic use of vaccine and serum in bacillary dysentery.

3. **Isolation and Release of Dysentery Patients and Suspects.**[9]— In outbreaks of some magnitude it is often difficult to keep track of patients or suspects, so that none with positive cultures are released from isolation. We have used a red isolation card, 6 by 5 inches (*i. e.*, two 3 by 5 inch index cards joined and perforated at the 5 inch side for ease in separation). *As soon as any patient is admitted with diarrhea or a history of recent diarrhea* the nurse attaches the half card marked "Isolation (D. P.)" to a conspicuous part of the bed. "D. P." refers to "dysentery precautions," the latter term being avoided for purely psychologic reasons. The back part of the card is marked "Instructions to Nurse" and clearly indicates that she is to (1) isolate the patient, (2) notify the epidemiologist at once by detaching the other half of the card, (3) send three fecal specimens to the laboratory on successive days and (4) release the patient from isolation only on receipt of the signed certificate of release. While this system was originally devised to prevent or control hospital outbreaks, its applicability is general, for the sooner persons with dysentery are isolated, the quicker the outbreaks terminate.

4. **Prophylactic Active and Passive Immunization.**—Observations during outbreaks or major epidemics strongly suggest the possibility of an acquired immunity to bacillary dysentery. Thus, during the Jersey City epidemic of 1934 the rise in incidence started about July 22, reached its peak on August 11 and then rapidly declined, so that by the end of the month the epidemic was practically terminated. A sharp secondary rise occurred, however, after Labor Day, when there was a marked influx of children returning from their summer vacations, and was confined chiefly to these newly arrived, nonimmune persons. Similar observations have been made by McGinnes and his co-workers[25] and others. While it is difficult to prove the point by laboratory methods, I believe that acquired immunity to bacillary dysentery is definite and probably lasts for a considerable time. I have often encountered country outbreaks in which the natives were relatively unaffected while the city vacationists proved virgin soil for the infection, which involved almost all new arrivals. In a study of the sus-

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* Formulated by the International and Pan-American Dysentery Registry and presented before the American Public Health Association in 1939.

ceptibility of the newborn to acute bacillary dysentery, Osofsky and I[17] found that in a group of 100 mothers and their infants there was practically no placental transmission of antibodies from mother to baby. We then studied a separate group of 10 mothers who had definite diagnostic titers at the time of delivery and found that in only one instance did the baby's titer remain at the diagnostic level after the seventh day. In two instances titers which equaled those of the respective mothers at birth fell to a complete absence of agglutination in any dilution by the eighth and the ninth day.

ISOLATION
(D. P.)

Upper half (front)

Instructions to Nurse
Any patient with a recent history of diarrhea or at the *first sign* of a diarrheal stool—isolate immediately and notify Dr. John Smith by attached card.

Upper half (back)

Notification of Diarrhea Case
Dr. John Smith:
Patient: Ward:
has been isolated because of diarrhea and will not be released until we are notified by you. Three fecal specimens on successive days are being sent to the laboratory for culture.
Date isolated:
Signed:————

Lower half (front)

Release from Isolation
The patient named on the reverse side of this card may now be released from isolation.
Date: Signed————————
Dr. John Smith
Fecal cultures: Three examinations on the following dates were negative for B. dysenteriae:——, ——, ——.
————————
Bacteriologist.

Lower half (back)

Fig. 142.—Representation of the card used for the isolation of dysentery suspects.

Although the number of agglutinins does not necessarily parallel the degree of immunity, the findings in Table 24 suggests that babies and young children are very susceptible to the disease, an impression supported by clinical experience. This susceptibility gradually diminishes with age in endemic areas, but a large group of young adults have never been exposed to the infection. With this hypothesis the question naturally arises, would it be wise either to expose them to the disease or to vaccinate them against it? Since the latter procedure is more practical and safe, we proceed to put it to the test, in spite of isolated, rather discouraging reports. Our investigation has been limited to the mannite-fermenting group, into which the organisms in the vast majority of cases fall. Since the lesions in bacillary dysentery are due to the toxin, one must depend largely on it for active immunization. I believe that the toxins differ even with the same strain, both qualitatively and quantitatively. I have been impressed also by the observation during prolonged outbreaks that even mild or abortive forms of the disease protect the patient against subsequent reinfection. Furthermore, immunization of rabbits with strains of relatively low toxicity usually made them refractory to subsequent injections of more toxic strains. Experiments are being carried out to test the accuracy of these observations and their applicability to mass immunization. Polyvalent Flexner strains are being used in doses of approximately one-third, one-half and one billion at five day intervals. Indigenous strains apparently afford the maximum degree of protection. In 10 cases repeated agglutination studies revealed marked rises in agglutination titer, particularly against the Mount Desert and Park-Hiss strains, reaching 1:320 or

Table 24.—Data Obtained in Follow-Up Agglutination Studies of 10 Breast-Fed Babies Whose Mothers Showed Titers of Diagnostic Significance

	Mother's titer*	Baby's titer at birth*	Days after birth	Baby's titer	Result
1	F, MD, PH 160	PH 40	58	PH 40	No increase
2	MD, PH 160	Negative	64	MD, PH 80	Increase
3	MD 160	MD 80	7	MD 160	Increase
4	MD 160, PH 80	Negative	8	PH 40	Increase
5	F, JC, MD, PH 160	MD 80	10	Negative	Decrease
6	MD, PH 160	MD 160	9	Negative	Decrease
7	MD, PH 160	MD 160	8	Negative	Decrease
8	PH 160	MD 40	8	Negative	Decrease
9	MD, PH 160	Negative	8	Negative	Negative
10	JC, MD, PH 160	Negative	8	Negative	Negative

Table 25.—Experimental Notes on the Prophylactic Immunization of White Mice Against B. Dysenteriae (Flexner 21)

1. *Immune Serum.*

(*a*) Intraperitoneal injection of 10 minimum lethal doses (M.L.D.) of *B. dysenteriae* (Flexner 21), followed *immediately* by the use of immune rabbit serum

No. of mice	M.L.D.	Immune rabbit serum, 0.5 cc.	No. died	No. survived
3	10	R 311	0	3
3	10	R 312	0	3
3	10	R 313	1	2
20	10	R 227	0	20
20	10	R 300	4	16
12	10	Normal rabbit serum	12	0

Summary: Of 49 mice receiving simultaneous injections of 10 M.L.D. of eighteen hour broth culture of *B. dysenteriae* and immune rabbit serum, 10.2 per cent died.

Of 12 mice receiving 10 M.L.D. of eighteen hour broth culture of *B. dysenteriae* but no immune serum, 100 per cent died.

(*b*) Passive transfer: Mice receiving immune serum at intervals of eighteen to one hundred and twenty hours *before* being inoculated with 10 M.L.D. of eighteen hour broth culture of *B. dysenteriae* (Flexner 21)

No. of mice	Immune serum	Interval in hours between injections of serum and culture	M.L.D.	No. died	No. survived
3	R 312	18	10	0	3
3	R 313	18	10	1	2
3	R 304	18	10	0	3
3	R 316	18	10	0	3
4	R 316	72	10	0	4
4	R 316	96	10	0	4
4	R 316	120	10	1	3
10	None	0	10	10	0
3	None	0	10	3	0

Summary: Of 24 mice receiving immune rabbit serum at intervals of eighteen to one hundred and twenty hours before inoculation with 10 M.L.D. of *B. dysenteriae*, 8.3 per cent died.

Of 13 control mice receiving normal rabbit serum or no serum before inoculation with 10 M.L.D. of *B. dysenteriae*, 100 per cent died.

Type specificity and effective immunization appear to go hand in hand. From a military standpoint, the use of T-P-D (typhoid-paratyphoid-indigenous dysentery strains) is suggested in proportions of 2.2.6. These antigens appear to act synergistically.

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* Strains of *B. dysenteriae* are indicated as follows: F, Flexner Y; JC, Flexner (Jersey City); MD, Mount Desert; and PH, Park-Hiss.

1:640 in almost every instance. In England, Paddle[27] reported the successful use of prophylactic vaccination in the Caterham Hospital, where Flexner dysentery has been endemic for many years. A similar report was made by Van Hoof[30] for the Belgian Congo.

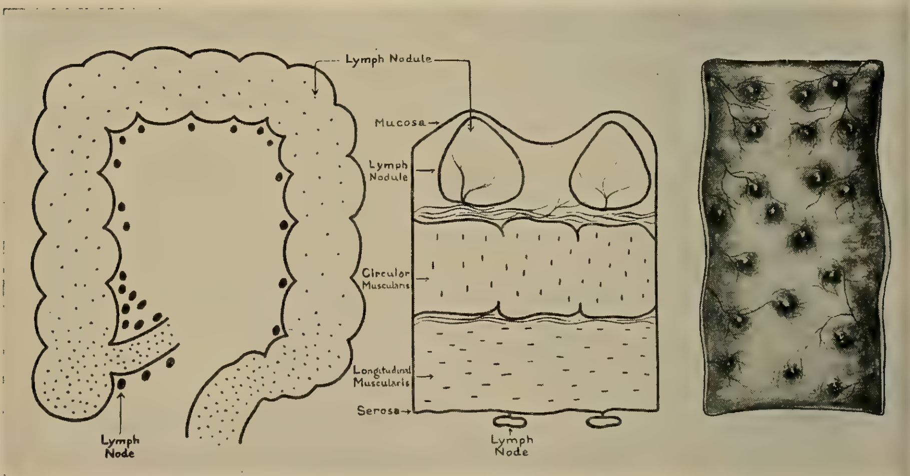
The use of serum for prophylactic passive immunization is of definite value during outbreaks. This may be obtained from patients who have recovered, or standard antidysentery serum may be used. The former procedure is more practical in epidemics and has the advantage of furnishing more type-specific serum. For accurate dosage the serum from recovered patients should be tested for protective action against the prevailing strain, which has been injected intraperitoneally into white mice. In this way pooled serum can be graded in terms of mouse units (*i. e.*, the amount of serum which will protect the mouse against one minimal lethal dose of the organism). From preliminary investigation it appears that approximately 25 cubic centimeters of potent immune serum injected subcutaneously is effective for several weeks—more than sufficient time to allow inoculation of all contacts. Prophylactic serum was efficacious during the 1936 epidemic of Shiga dysentery in Saskatchewan, which involved 146 persons, with 29 deaths (19.8 per cent).[2]

Experimental studies in active and passive immunization[18] lend further support to the applicability of these methods in the prevention of bacillary dysentery (Table 25).

CURATIVE AND SUPPORTIVE THERAPY OF ACUTE BACILLARY DYSENTERY

Spontaneous recovery from the mild form of the disease usually occurs without the use of serum or drugs. The more severe types require curative and supportive medical care. The principles of therapy, based on certain fundamental concepts of pathogenesis, may be summarized as follows:

Stage 1

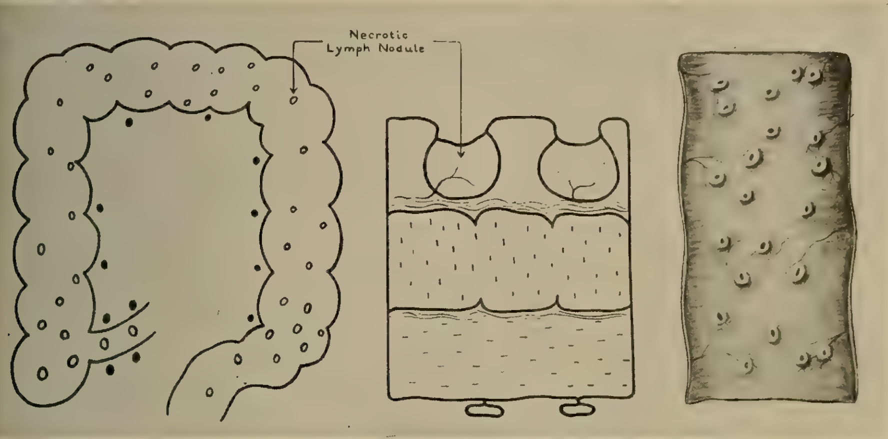


Congestion, Hyperemia and Lymphoid Hyperplasia

Fig. 143.—Diagrammatic sketches showing transition stage 1 from acute bacillary dysentery to chronic distal ileitis, chronic ulcerative colitis and nonspecific granuloma.

Therapy involves elimination of the causative organism, specific neutralization of absorbed toxins and the use of an adequate diet. Diarrhea in acute bacillary dysentery represents the body's effort to eliminate the pathogenic organisms and their toxins. If it is induced or facilitated *at the onset,* the disease may be aborted, its course shortened or its severity lessened. For this purpose, a single dose of castor oil at the onset of the disease is advisable. The following sulfonamide drugs are of value, probably in decreasing order of effectiveness: succinylsulfathiazole, sulfathiazole and sulfaguanidine. This evaluation takes into account the greater absorbability of the two latter drugs and its attendant danger. In general,

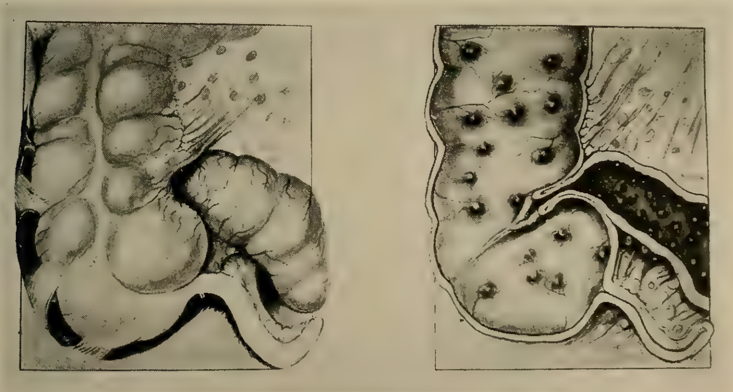
Stage 2



Focal Lymphoid Necrosis With Superficial Ulceration

Fig. 144.—Diagrammatic sketches showing transition stage 2 from acute bacillary dysentery to chronic distal ileitis, chronic ulcerative colitis and nonspecific granuloma.

Stage 2a

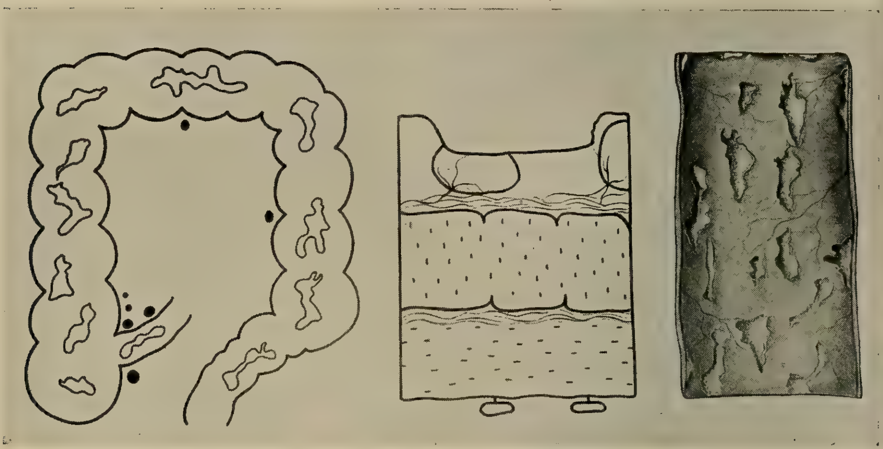


Acute Distal Ileitis With Mesenteric Lymphadenitis

Fig. 145.—Diagrammatic sketches showing transition stage 2a (the same as stage 2 except that the most prominent change is in the ileum) from acute bacillary dysentery to chronic distal ileitis, chronic ulcerative colitis and nonspecific granuloma.

adequate amounts of a poorly absorbed sulfonamide compound used within the first twenty-four hours for Flexner infections appear to give the best results. For adults with the average, moderately severe type, 2 Gm. four times daily during the first three days of the disease appears to be adequate. The dose is then halved until the stools are bacteriologically negative. There appears to be some evidence that the use of sulfonamide drugs has increased the number of carriers and the frequency of recurrences.

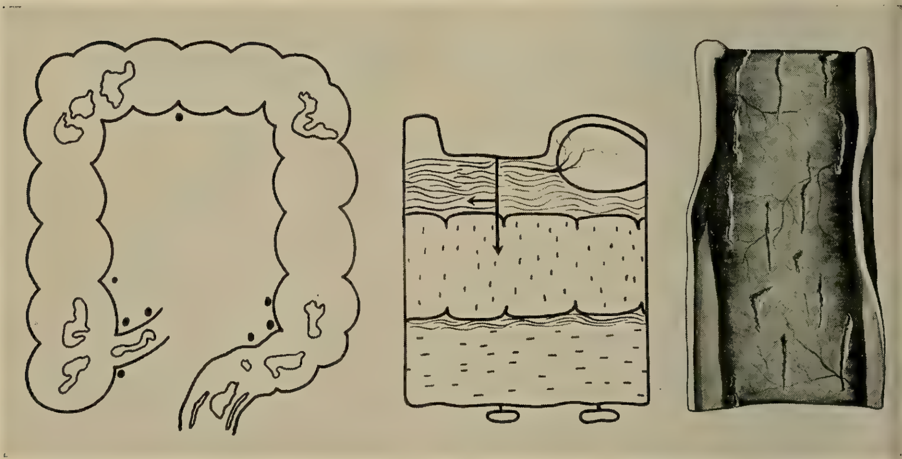
Stage 3



Confluent and Deep Ulceration

Fig. 146.—Diagrammatic sketches showing transition stage 3 from acute bacillary dysentery to chronic distal ileitis, chronic ulcerative colitis and nonspecific granuloma.

Early Stage



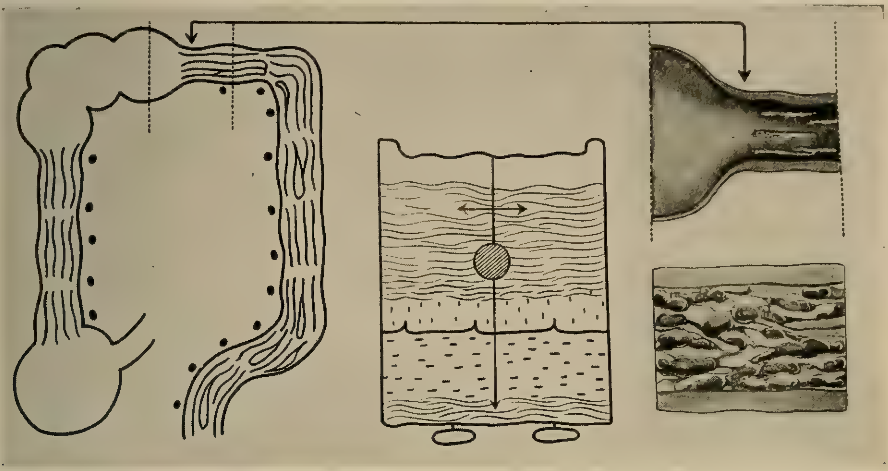
Destruction of Lymph Nodules; Secondary Intramural Infection

Fig. 147.—Diagrammatic sketches showing transition from acute bacillary dysentery to chronic ulcerative colitis (early stage).

Bacteriophage has proved rather disappointing as a therapeutic agent in bacillary dysentery. It appears to be most beneficial when used early in the disease and in adequate doses against susceptible dysentery strains.

The use of bacterial antagonists holds some promise for both prophylaxis and cure, but requires further study. I have isolated nonlysogenic *B. coli* strains which completely prevented the growth of dysentery organisms *in vitro*, even when the proportions were ninety-five of the latter to five of the former.

LATE STAGE



MURAL FIBROSIS, PSEUDOPOLYPOSIS, ULCERATION

FIG. 148.—Diagrammatic sketches showing late stage of chronic ulcerative colitis. Note the deep ulceration of the mucosa, the disappearance of lymph nodules and intramural abscess formation (*arrows*).

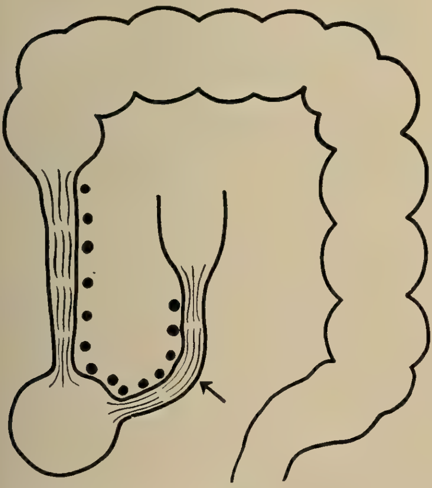


FIG. 149

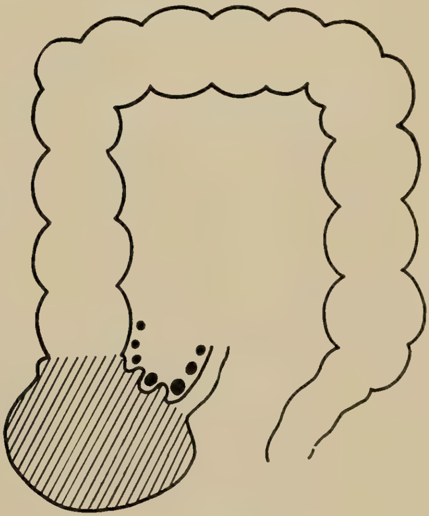


FIG. 150

FIG. 149.—Diagrammatic sketch of combined form of chronic distal ileitis (*arrow*) and chronic ulcerative colitis, showing a persistent acute lesion in stage 2a.

FIG. 150.—Diagrammatic sketch of nonspecific granuloma, showing a productive type of inflammation.

Antidysentery serum is most effective for Shiga-Kruse infections and when used in adequate doses during the first twenty-four to forty-eight hours. Monovalent type-specific serum from convalescent persons often is strikingly beneficial for all types of acute bacillary dysentery.

Nutrition is hardly a major concern in the average case. When the disease is prolonged or severe, however, the loss of fluid and electrolytes and poor intake and absorption of all the other essential food elements, including vitamins, is pronounced and requires adequate replacement. Fluid and salt balance can be readily maintained by the parenteral use of 5 per cent dextrose in physiologic salt solution or Ringer's solution. Hypoproteinemia is rarely marked and can be modified by the use of plasma or whole blood. Starvation has no valid basis in the treatment of bacillary dysentery. The modern tendency is to emphasize smooth bulk, fluids, carbohydrates and vitamins. The R B T (rice-banana-tea) diet, with a moderate amount of protein added in the form of egg albumen water, conforms to this practice.

Palliative drug therapy involves the use of three types of drugs: (1) those which act locally in the intestine as adsorbents, protective coatings, antiseptics, bacteriostatics, astringents or cleansing agents (few have any valid scientific basis to recommend their use); (2) those which act on the central or peripheral nervous system (crude opium is perhaps the most useful, but should never be continued until complete cessation of diarrhea); and (3) those which serve for replacement, principally fluids, minerals and vitamins administered parenterally.

R B T Diet (Felsen)

For............................
Date............................

1. *Acute Phase*

Rice: Soft boiled; strained rice water; puffed rice.
Banana: Ripe with brown spots. Whole, mashed or as banana powder ("meletose").
Tea: Preferably green.
Supplementary items: Egg albumen water (whites of twelve eggs to 1 quart of water and flavor with lemon or orange juice), water, clear broths (vegetable, beef, clam), skimmed boiled milk. Use lactose or "dexin" (Burroughs-Wellcome) for sweetening, 4 oz. daily.

Directions:
1. Total daily fluid intake should at least equal output.
2. All food to be taken warmed or at body temperature.
3. Rice-banana-tea feedings thrice daily with additional fluids at 10 A. M. and 3 P. M. unless otherwise indicated.

2. *Receding Phase*

Add daily in the order stated:
1. One soft boiled or poached egg, dry toast, Holland rusk, beef juice, strained oatmeal.
2. Potato (boiled, mashed or baked), one broiled lamb chop, one-half cube of butter, additional egg.
3. One teaspoonful of cane sugar or honey, tender broiled steak, puréed peas.
4. Chicken (broiled or boiled).
5. California red wines, boiled spaghetti or macaroni.
6. One serving of coffee with little cream, corn flakes with boiled and cooled whole milk.
7. Two cubes of butter, roast beef.

Directions: Eat slowly; masticate well; three feedings daily plus water or broth at 10 A. M. and tea at 3 P. M.

Special instructions may be given in individual cases.

CLINICAL AND LABORATORY NOTES CONCERNING THE RELATION OF CHRONIC DISTAL ILEITIS AND CHRONIC ULCERATIVE COLITIS TO ACUTE BACILLARY DYSENTERY

I wish to record herein in summary form the evidence which I have accumulated* to support my contention that chronic distal ileitis and chronic ulcerative colitis are but late manifestations of the same disease, bacillary dysentery. Similar evidence on chronic ulcerative colitis has been presented by a number of other investigators.[24]

1. **Clinical Data.**—(*a*) Observation of acute inflammation of the distal part of the ileum as an early manifestation of bacillary dysentery in 29 instances.[8]

(*b*) Observation of different stages of the disease *in the same person.* The development of chronic distal ileitis from the acute form has been seen in 14 instances. Chronic ulcerative colitis following an attack of acute bacillary dysentery has been seen in 25 instances. Although originally observed sporadically, the follow-up studies after the Jersey City epidemic of 1934 afforded a splendid opportunity to learn the natural course of the disease uninfluenced by specific therapy.[14] For the first time patients involved in a major epidemic have been followed for a reasonable period *after* the subsidence of the epidemic. As will be seen from Table 26 and 27, 1 of every 3 patients originally studied during the epidemic of 1934 had persisting or recurring symptoms and signs of intestinal involvement, and 1 of every 10 patients had roentgenographic, sigmoidoscopic or pathologic evidence of chronic ulcerative colitis or distal iletis.

Table 26.—Chronic Symptoms Nine to Twelve Months After an Attack of Acute Bacillary Dysentery

Total number of hospitalized patients		210
Total number of patients followed		122
Persistent or recurrent symptoms and signs		46 (37.7%)
Diarrhea with blood, mucus and pus	8 (6.5%)	
Watery diarrhea without gross blood	12 (9.8%)	
Bloody evacuations without diarrhea	3 (2.4%)	
Miscellaneous intestinal symptoms	23 (19.0%)	

Table 27.—Visible Evidence of Ulcerative Colitis or Ileitis in Follow-Up of 122 Cases of Acute Bacillary Dysentery

(*a*) Patients with roentgenographic evidence of chronic ulcerative colitis	8 (6.5%)
(*b*) Additional patients with sigmoidoscopic evidence of chronic ulcerative colitis	2 (1.7%)
(*c*) Chronic distal ileitis (observed in 2 at operation, 1 at necropsy)	3 (2.5%)

2. **Epidemiology.**—(*a*) The general geographic distribution of chronic ulcerative colitis and distal ileitis appears to correspond to that of bacillary dysentery. The increasing observation of these diseases in recent years appears to parallel the increasing incidence of acute bacillary dysentery.

(*b*) Contact infection in chronic distal ileitis or ulcerative colitis occurs chiefly during the stage of acute bacillary dysentery, when the specific organism is present in the intestines. The incidence of contact infection in my series of cases of chronic disease was 37.4 per cent, a high figure since the original source of infection is often difficult to determine after one or more years have elapsed.

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* The figures given in the summary are as of June 19, 1936, and cover the period from September 1933 to June 1936. Further experience has merely served to duplicate my earlier observations.

(*c*) Conjugal infection is relatively common if mating occurred prior to the onset of the original attack of bacillary dysentery or if one partner, involved prior to marriage, still harbors the organism.

(*d*) There is no strictly seasonal incidence of bacillary dysentery in the North Temperate Zone.

3. **Serology.**—Diagnostic agglutination titers on the serums of patients with chronic ulcerative colitis or distal ileitis have been obtained in 93.5 per cent of 124 cases, as compared with 4.6 per cent of a control group of 300.

4. **Bacteriology.**—Positive cultures for *B. dysenteriae* were obtained in 14.2 per cent of 70 cases of chronic ulcerative colitis or distal ileitis. This finding is significant since positive cultures are unusual after the first or second week of acute bacillary dysentery. Bacteriophage for *B. dysenteriae* was obtained in 39.2 per cent of 51 cases studied. Of 100 control cases, bacteriophage was found in 1.

Crypt aspiration material is better than feces for culture.[12] To obtain this I use a heavy-walled capillary glass tube (5 millimeters outside diameter, 35 centimeters length). A fusiform dilatation, sufficient to hold three or four drops of fluid, is blown into the tube about 2 centimeters from the distal end, which is bent slightly for better approximation to the bowel wall. The tube is inserted through the sigmoidoscope and applied directly to the mucosa. The material obtained by suction with a bulb or suction pump is sprayed directly on a fresh Endo plate. Isolated colonies are readily picked off after over-night incubation.

5. **Pathology.**—In order to understand the pathologic lesions in chronic ulcerative colitis and ileitis it must be remembered that in acute bacillary dysentery any part of the small or large intestine may be involved, independently or concomitantly. "Skip areas" of segmental inflammation occur. The sites of predilection, however, are the distal part of the ileum and of the colon. The pathologic changes of acute bacillary dysentery have been described. With the chronic form of the disease the patient recovers partially or temporarily, only to suffer periodic remissions and exacerbations. The ulcerations originally produced by the toxin of *B. dysenteriae* persist; secondary nonspecific intramural infection occurs, and in an attempt at healing, extensive intramural fibrosis takes place. The lymph nodules are largely destroyed, and islands of intact mucosa interspersed with geographic, linear or serpiginous areas of ulceration eventually line the bowel lumen. The mucosa may assume a polypoid form due to edema and retained secretion. In the ileum or cecum a granulomatous type of lesion may be encountered and is the result of a productive inflammatory process. The presence of giant cells may suggest tuberculosis, but specific stains and guinea pig inoculations with the macerated tissue give negative results. In general, the end-result is an ulcerated, narrowed, thickened and infected vascularized tube of connective tissue. In the ileum sinus tracts may form, owing to extension of the infection from an affected portion of bowel to adjacent loops. Whether the process occurs in the ileum or colon, it has the same underlying pathogenesis and represents the late stage of bacillary dysentery. Intramural or extramural abscesses may form, the former characterized clinically by a septic type of temperature curve, which falls abruptly when the abscess empties itself into the lumen of the bowel.

The roentgenographic findings are due to the pathologic changes described. Thus, in the ileum there is Kantor's "string sign," due to extreme narrowing of the lumen by scar tissue and fistulous tracts; in the colon there occur obstructive lesions (defects) at or near the ileocecal region, owing to granuloma formation, irregularities of mucosal pattern or pseudopolyposis associated with ulceration and loss of haustration or stenosis due to chronic inflammation with intramural fibrosis.

6. **Diagnosis of Chronic Bacillary Dysentery.**—(*a*) The *epidemiologic* criterion is a history of contact infection at the time symptoms *first* appeared.

(*b*) *Clinical* signs are persistent or recurring attacks of abdominal cramps and diarrhea; sigmoidoscopic evidence of ulceration, pseudopolyposis or mural fibrosis with stenosis; palpation of a tender, thickened or spastic ileum or sigmoid flexure; "mendicant's posture" on standing or walking; chronic arthritis, the exacerbations being associated with periodic attacks of diarrhea. "Mendicant's posture" refers to a peculiar position of the body and a characteristic gait of ambulatory patients during the acute exacerbation of intestinal symptoms. It disappears completely during the remission stage. The patient is generally emaciated and dehydrated from frequent watery evacuations. His pallor, hollowed cheeks and sunken temples form an almost funereal background to an expressionless face or to a worried look which betokens great physical discomfort. In walking there is exhibited a peculiar shuffling gait, the cervical and the dorsal spine being bent forward and held rigid. The shoulders are high, the head bowed and the abdomen somewhat concave. The patient appears to be looking at the ground and only casually glances upward at passers-by, without moving his head. One hand is held on the midsection or on the hip. It seems as though only a distaff would be required to complete the picture of the proverbial beggar, portrayed by Edouard Manet in *Le Mendiant*. The chief differences, however, are that Manet's figure is that of an old man who is well, and the posture is permanent. The subject with this disease, on the other hand, is generally young and sick and the posture temporary.

(*c*) *Roentgenographically,* there are defects in mucosal pattern; loss of haustration; narrowing of the bowel lumen; presence of the string sign with ileal disease, and an intrinsic obstructive lesion (granuloma).

(*d*) In the *laboratory,* the culture of *B. dysenteriae* from crypt aspirations or mucosal scrapings, diagnostic bacteriophage in the feces and a diagnostic agglutination titer of the blood are the important points. The skin test for sensitivity to the dysentery antigen and examination of smears from the intestinal wall for the characteristic cytologic features may be used as supplementary aids in diagnosis.

7. **Therapy of Chronic Bacillary Dysentery.**—The ideal treatment of chronic distal ileitis (regional enteritis) and chronic ulcerative colitis is *the prevention of acute bacillary dysentery.* In view of the widespread prevalence of the acute disease, one's efforts must also be energetically directed toward preventing the chronic phase. I therefore stress:

(*a*) The routine active immunization with D-C vaccine of all patients recovering from acute bacillary dysentery. Pathologic studies suggest that even with acute disease some nonspecific intramural invasion occurs. With this in mind I use combined autogenous and stock strains of *B. dysenteriae*, hemolytic and nonhemolytic *B. coli* and *Enterococcus* to a total concentration of one billion organisms per cubic centimeter. Six injections are given in three weeks in gradually increasing doses, to a maximum of 1 cubic centimeter for adults. *All patients with acute bacillary dysentery should be reexamined at regular intervals for one year,* the period within which chronic dysentery usually becomes manifest.

(*b*) For chronic bacillary dysentery I prescribe rest, high calorie, high vitamin diet, D-C vaccine and antivirus therapy, intestinal oxygenation and, where necessary, repeated transfusion. Local intestinal medication is usually valueless and often harmful. Theoretically, these patients must be treated by the same route through which the original disease progressed, *viz.,* the systemic route. Antidysentery serum as a specific therapeutic agent is of little or no value for chronic bacillary dysentery.

Dietary limitations based on minimal residues are of limited usefulness, except for patients with chronic distal ileitis who have subacute obstruction or do not masticate the food thoroughly. The average patient soon acquires an aversion for the "smooth" diet and defeats the purpose which the physician sets out to accomplish—his general systemic upbuilding. That a well masticated food residue produces mechanical irritation of ulcerated mucosa is hardly supported by careful clinical observation. During the diarrheal phase three meals daily are better than frequent small meals, as eating almost invariably incites a bowel movement.

D–C DIET (FELSEN)

Main Group

Group A.* *Vegetables:* Artichoke, asparagus, bean (green), beet greens, broccoli, Brussels sprout, carrot, chard, collard, corn, dandelion greens, escarole (chicory), kale, lamb's quarter, lettuce, okra, parsley, pea, green pepper, sweet potato, spinach, squash (Hubbard), squash (summer), tomato, turnip greens, watercress.
Fruit: Cherry, mango, avocado, banana, papaya, peach, prune, cantaloupe (muskmelon).
Meat and Fish: Beef liver, fish roe.
Miscellaneous: Butter, cream, cream cheese, American cheese, Cheddar cheese, egg or egg yolk, whole wheat bread, cornmeal, cod liver or halibut liver oil.

Group B. *Vegetables:* Dried bean, cauliflower, chard, lentil, green pea, soy bean.
Fruit: Avocado.
Meat: Liver, lean pork, bacon, chicken, ham, lamb chops.
Miscellaneous: Buckwheat, whole grain, peanut butter.

Group C. *Vegetables:* Artichoke, asparagus, bean (green), beet, beet greens, broccoli, Brussels sprout, cabbage, cauliflower, celery, chard, collard, corn, cucumber, dandelion greens, endive, escarole, garlic, kale, kohl-rabi, leek, lettuce, vegetable marrow, okra, parsley, parsnips, green pea, green pepper, potato, rhubarb, spinach, tomato, turnip, turnip greens, watercress.
Fruits: Currant, gooseberry, loganberry, grapefruit, lemon, lime, orange, pineapple, strawberry, tangerine, guava.
Meat and Fish: Beef brain, beef liver, clam.

Group D. *Meat and Fish:* Liver, salmon, sardine.
Miscellaneous: Egg or egg yolk.

Group G. *Vegetables:* Beet greens, eggplant, kale, turnip greens.
Fruit: Prune.
Meat and Fish: Beef liver, beef (chuck, loin or steak), lamb chop, mutton, veal cutlet, ham, heart, kidney, herring, sardine.
Miscellaneous: Cheese, egg or egg yolk.

Note: In groups B and C boiled vegetables should be cooked in closed pots. The fluid as well as the vegetable should be used.

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* Letters refer to vitamin group. The foods specified are rich in the vitamin specified.

Calcium group: Asparagus, bean, broccoli, cauliflower, cheese, cream, egg yolk, kale, sardine, turnip greens.
Iron group: Dried bean liver, egg yolk, heart, soy bean, beet greens, asparagus, chard, pea, oatmeal, parsley, turnip greens, whole wheat.

Supplementary Group

Flour products: Toast, stale white bread, Holland rusk, soda crackers, spaghetti, macaroni. Rice flour should be used for thickening.
Cereals: Rice, puffed rice, puffed wheat, cream of wheat, corn flakes, oatmeal.
Desserts: Cornstarch pudding (vanilla or chocolate), jello or similar gelatin, rice pudding, bread pudding, sponge cake, custard, junket, apple butter.
Beverages: Tea chiefly. Coffee with little cream or cocoa without milk, sparingly.
Broths: Beef, vegetable, oyster, clam (flavored, if desired, with thyme); no condiments.
Sweetening: Cane sugar, honey, milk sugar, "dexin" (Burroughs-Wellcome).

Prepared Strained Foods

(Heinz or similar)

Apricots and apple sauce, beef and liver soup, carrots, cereal, green beans, mixed greens, peas, spinach, tomatoes, tomato juice, vegetable soup.

General Rules for the Patient's Guidance

1. Relax mentally and physically. Be cheerful. Have a hobby.
2. Rest for one hour after eating.
3. Three regular daily meals except for water or tea at 10 A. M. and 3 P. M.
4. All fluids and solid food should be eaten at or near body temperture or warmer. Total fluids for adult must at least equal output. The average adult should consume 2 to 3 quarts daily.
5. Eat slowly and masticate thoroughly. The intestine must "chew" food improperly prepared by the teeth.
6. Eat at least two ordinary portions daily from groups A, B, C; one portion daily from groups D, G.
7. Eat one portion daily from the calcium or iron group, in rotation.
8. If desired, add selections from "supplementary group."

Special Instructions:

1. Brewer's yeast, 1 teaspoonful, three times daily in a little tomato juice.
2. Red meats (roasted, boiled or broiled) twice daily, if possible.
3. No milk.

D-C vaccine and antivirus are used for active immunization. The former is given in twenty-seven injections in gradually increasing doses for ten weeks. A smaller series of twelve injections is then given every six months for three years. I use a modified Besredka antivirus containing the same organisms as the D-C vaccine, in 1 ounce doses *per rectum* thrice weekly. A simple routine is the use of vaccine on Monday, Wednesday and Friday and of antivirus on Tuesday, Thursday and Saturday, with rest on Sunday. Exacerbation of intestinal symptoms may be caused by the antigen and can usually be controlled by the use of deodorized tincture of opium.

Intestinal oxygenation[4] is used to control the anaerobes the toxins of which are absorbed through the denuded areas, to promote drainage of aerobes from the interstices of the intramural structures and to quiet excessive intestinal peristalsis. The beneficial effects of oxygen are often rather startling in the presence of toxemia. Approximately 250 cubic centimeters three to six times daily is given with a no. 16 soft rubber catheter. Since the bowel wall acts as a membrane diffusible in either direction, oxygen administered by inhalation will also enter the intestine from the blood stream. I have used the respiratory route for several years for patients who have painful anal fissures or pararectal abscesses.

Repeated transfusions, particularly from donors who have recovered from dysentery, and the routine use of emetine for chronic dysentery, to guard against a coëxisting amebiasis, are advisable.*

Surgical intervention, particularly resection, is contraindicated, except as an emergency procedure. The operator generally cuts through infected bowel wall or overlooks "skip areas," with the result that recurrences are common. Intramural abscesses generally empty spontaneously through the mucosa into the lumen of the bowel. Those that approach the serosa excite, long in advance of perforation, a productive type of inflammation which usually effectively walls off the infection. A localized peritonitis may occur and is generally accompanied by a high, septic type of temperature curve, with marked pain, tenderness and muscular rigidity. The typical Hippocratic facies may develop and the patient appear dehydrated and overwhelmed by a severe toxemia. A large mass may be felt at the site of the disease, and it requires great courage to keep from operating on the abdomen. Almost invariably, however, surgical intervention results in generalized peritonitis and death, while conservative medical treatment is often followed by a surprising recession of the inflammation in one to three weeks. Follow-up studies for two to three years in a number of cases have shown complete disappearance of the mass and apparent restitution of the bowel to normal. The acute obstructions which occasionally occur with long-standing chronic distal ileitis must be treated like any other acute obstruction. The more frequent subacute or chronic obstruction of the distal part of the ileum had best be treated as I have outlined before surgical intervention is considered. In 5 instances the obstructive symptoms and signs disappeared, as shown clinically and by follow-up roentgen studies. Unless future developments in surgery can overcome the anatomic and pathologic difficulties inherent in these two diseases, the treatment of chronic distal ileitis and ulcerative colitis remains essentially medical. Not only that, but if my concept of their pathogenesis is correct, *the ideal treatment is the prevention of bacillary dysentery.*

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* In this section the author fails to take into consideration that large group of patients with recurring diarrhea whose blood shows high agglutination titers for the various organisms with little or no change in the lining of the bowel, and who show prompt relief following graduated injections of vaccine made from the offending organisms.—EDITOR.

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CHAPTER XXX

NONSPECIFIC OR INDETERMINATE ULCERATIVE COLITIS

Definitions.—A colitis is any regional, segmental or general involvement of the large intestine including the rectum resulting in a sanguineous, a mucosanguineous, a mucopurulent or a mucopurulent, sanguineous discharge, with or without frequency in defecation and due to known or unknown factors, save neoplasms and diverticulitis.

Ulcerative colitis is due to a single or to multiple unknown factors. Its pathologic structure is not pathognomonic, and it appears as a syndrome: a constant set of symptoms occurring together with a sum of signs of a morbid state.

It is also known as idiopathic ulcerative colitis, nonspecific ulcerative colitis, indeterminate ulcerative colitis, colitis ulcerosa, colitis gravis, primary ulcerative colitis and suppurative colitis. The term thromboulcerative colitis has recently been suggested. This tends to confuse the problem, since the cause is undetermined and the thrombotic phenomena are not pathognomonic, contrary to the specific implications of this name.

To avoid ambiguity, the following terms employed in this chapter are defined as follows:

Diarrhea: frequency of defecation with ill formed dejecta but without blood or pus.

Dysentery: frequency of bowel movement with blood and often pus.

Intermission: complete subjective and objective cessation of ulcerative colitis activity; arrest.

Remission: partial cessation of such activity.

Exacerbation: an increase of activity in the face of incomplete cessation.

Recurrence: reactivation of completely healed or arrested ulcerative colitis.

Extension: involvement of an additional bowel segment for the first time.

An enteritis is any inflammation of the small intestine due to known or unknown agents except that associated with a neoplasm. Diarrhea or dysentery may or may not be a feature. However, blood and pus will usually be seen microscopically and blood chemically, if not microscopically, in the intestinal discharge. When the condition is restricted to the ileum, it is known as an ileitis.

An irritable digestive apparatus is one that functions poorly, evidenced by changes principally in tone or motor activity and to a lesser extent in secretion. The disturbance when restricted to the colon is known as "irritable colon." It is not colitis, but unfortunately it is often so designated. The term spastic colon, by which the irritable colon is frequently designated, is inexact, since rarely is the purely functionally disordered large bowel wholly spastic, spasm and atonicity usually manifesting themselves simultaneously in the same colon.

ETIOLOGY

Distribution—Incidence.—This syndrome is not known to occur spontaneously in animals. In man it is not restricted to any race, age, sex, season or zone. At the Johns Hopkins Hospital the cases appear to be divided about equally between the sexes, the onset in the greatest number falling within the second and fourth decades. The disease is seen infrequently in children and rarely in a septuagenarian or octogenarian. The disease appears to be growing more prevalent, and improvements in diagnostic acumen and methods or even the avoidance of the erroneous diagnoses heretofore common cannot be held wholly responsible. However, the number of cases in the general population still is small.

Epidemiology.—Nonspecific or indeterminate ulcerative colitis possesses neither epidemic nor infective properties. Its lack of transmissibility is striking. The records of the Johns Hopkins Hospital reveal 4 instances of more than one occurrence in a family.

Immunity.—No known prophylactic measure protects from an attack. No therapeutic measure protects from a subsequent one. No attack is a safeguard from recurrence, exacerbation or extension. In short, no active or passive immunity is acquirable.

Predisposing Factors, So-called.—Various authors have pointed out the relative concomitance of initial symptoms and exacerbations with other factors, infections of the upper part of the respiratory tract, epidemic diarrhea (in all likelihood bacillary dysentery) or diarrhea following the drinking of polluted water, as well as amebic dysentery and the use of measures which act locally by reducing bowel resistance, such as enemas and laxative medication. Similarly, the psychiatric aspects, because of the occurrence of ulcerative colitis in some young men and women of tense, overly sensitive and emotionally unstable tendencies have come into consideration of late.

By definition, a proved bacillary or amebic dysentery or a bacillary dysentery persisting after the disappearance of the organism is not an indeterminate or nonspecific ulcerative colitis. Also, at present, there is no way of establishing whether a persisting colitis following eradication of associated infection with *E. histolytica* on institution of adequate therapy was initiated by this protozoön (*vide infra*).

Parasitology.—The very definition of this syndrome precludes the presence of pathogenic parasites. Only two parasites are known to produce a true colitis: the intestinal protozoön *E. histolytica,* an ameba, and *Bal. coli,* a ciliate. The latter, particularly in the temperate zone, is a medical curiosity. The relation of *E. histolytica* to ulcerative colitis is in a measure determined by the response to specific therapy. If there is *complete,* not partial, response *subjectively and objectively* to amebicidal therapy coincidental with the eradication of the parasite, then it may be said that there was a cause and effect relation between parasite and host manifestations. Present medical knowledge does not permit the etiologic evaluation of *E. histolytica* in the production of colitis when on adequate exhibition of amebicides and the disappearance of the parasite there is either no clinical response or a partial one (Paulson and Andrews). Complement fixation as a diagnostic measure in amebiasis is not sufficiently refined for routine clinical use (Paulson and Andrews).

Bacteriology.—So far, there has been no adequate substantiation of any of the views expressed in regard to a bacterium as the specific cause of this condition.

The uncommon bacterial types, *Bacillus proteus, Bacillus pyocyaneus, Bacterium lactis aerogenes* and *Bacillus mucosus capsulatus* have been incriminated as etiologic agents in chronic ulcerative colitis (Jex-Blake and Higgs), but actually no satisfactory evidence has been adduced that any of these organisms bears any essential relation to this condition. *Bacillus paratyphosus B* has been isolated from intestinal lesions in occasional cases of ulcerative colitis and has therefore been regarded in those cases as a significant factor.

There is no satisfactory direct evidence for the belief that *Bacillus welchii* is of etiologic significance in ulcerative colitis. *Bacterium necrophorum*, strictly an anaerobe, may play a contributing or important secondary role in this disease. Normally, the organism is found in animals and man rarely or in small numbers. In the presence of ulcerative colitis, it is encountered abundantly; after ten days, there are specific agglutinins in high titer; during arrest few or no organisms can be isolated and the specific agglutinins are not present in significant titer. The bacterium produces abscesses in rabbits and is found in the presence of necrotic states in animals and man. Preceding factors influencing multiplication of *B. necrophorum* are not understood. No new studies of the etiologic relation of this organism to this disease have been reported. This evidence is well summarized by Dack, Kirsner, Dragstedt and Johnson.

Beta-hemolytic colon bacilli, almost never isolated from the normal colon, are occasionally encountered in the presence of ulcerative colitis (Torrey). This unusual presence suggests a contributing or secondary role, but does not prove it.

The view that indeterminate ulcerative colitis is an aberrant form of bacillary dysentery persists in England, on the Continent, in Canada and to a much lesser extent in this country. The arguments in favor of this view are: (1) Both may occur sporadically. (2) Both are noninfective as chronic states. (3) While in indeterminate ulcerative colitis no dysentery organisms are found, in chronic bacillary dysentery they are often not encountered, and when discovered there is a marked disparity between their paucity and the severity of the process. (4) The consensus now is that for either condition serum agglutination reactions are of no diagnostic import,* being only presumptive at best in bacillary dysentery. (5) As noted elsewhere, the pathologic picture, clinical course, location of lesions, sequelae and complications of the two may be indistinguishable. Felsen in support stated: "The development of chronic ulcerative colitis following an acute attack of bacillary dysentery in the same individual has been seen in 25 instances." However, in only 5 were dysentery organisms isolated, and in these during the acute phase. Of 112 patients studied nine to twelve months after the Jersey City epidemic of bacillary dysentery, Felsen found 46 (37.7 per cent) to have persistent or recurring intestinal symptoms or signs. Such data are in need of confirmation. In this connection, Portis reported recurrent diarrhea due to dysentery organisms.

On the other hand, the isolation of dysentery organisms in cases of what otherwise would have been designated as chronic ulcerative colitis varies from none (Copeland and Bargen) to 12 per cent (Winkelstein) to 20.4 per cent (Mackie). The transition to the chronic state from acute bacillary dysentery, reported by other observers, varies from less than 1 per cent (Brown and Bargen) to 5 per cent (Lensden, cited by Penner).

The arguments against the identity of ulcerative colitis and bacillary dysentery are: (1) The rare dysentery bacilli found and the severity of the chronic lesion make the causal relation of the former to the latter somewhat incredible. (2) The failure to isolate dysentery organisms more frequently cannot be explained wholly by their disappearance early in the course, the shortcomings of isolation methods, the unstable fermentation reactions of these organisms and differences and inconsistencies in their agglutinability with specific serums. Those in favor of the identity of ulcerative colitis and bacillary dysentery will deny the conclusion of the first postulate and use the second to point out the difficulties in establishing the presence of the bacterium as an adequate reason for its frequent absence, particularly in the chronic state. Incidentally, the failure to isolate dysentery organisms in patients with chronic bacillary dysentery and in some patients who in consequence of this are classified as having nonspecific ulcerative colitis is suggested—at least in part—by *in vitro* experiments. These indicate that adequate quantities of fresh blood (such as are encountered in the presence of dysentery) are deleterious to survival of the organisms (Paulson).

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* My clinical experience does not coincide with this point of view.—EDITOR.

The problem of differentiating between ulcerative colitis and bacillary dysentery at present involves the solution of certain technical phases: difficulties in isolation of *Shigella dysenteriae* Flexner and Sonne, the unstable responses of the organisms to some of the present identification methods and inadequacies of diagnosis by serum agglutination and with antidysentery bacteriophage. The extent to which these two conditions are or are not parts of the same disease may not be fully decided until procedures are made more dependable and criteria more uniform. Certainly the evidence shows that a definite, small and variable number of cases which were or might have been easily classified as instances of chronic ulcerative colitis appeared to be cases of chronic bacillary dysentery, and that in a small proportion of cases acute bacillary dysentery may pass into the chronic stage, often being indistinguishable from chronic ulcerative colitis. In the meantime, most American workers seem to feel that a colitis not associated with known epidemic bacillary dysentery, and one from which no pathogenic agent (now including the virus of lymphogranuloma venereum) can be isolated, is nonspecific ulcerative colitis and not bacillary dysentery.*

Cocci (diplococci, enterococci, streptococci and pneumococci) have been incriminated as prime etiologic agents.

A diplococcus may be a pneumococcus, an enterococcus or one of many varieties of streptococcus. When observed in young cultures in liquid mediums, when smeared from solid mediums or from material secured directly from the bowel, the organism—even the streptococcus which in older liquid cultures or in subcultures may present characteristic chains—appears as a diplococcus. Occasionally diplobacilli, diphtheroids, staphylococci and small, plump Gram-positive bacilli on direct smear or from early cultures in liquid mediums, especially when the cultures are mixed, may be indistinguishable from diplococci. Obviously, then, a diplococcus is not distinctive; the structure is not characteristic—it is merely descriptive. The use of terms such as "diplococcus" and "diplostreptococcus" to designate specific organisms is therefore an error, for they denote characteristics common to several types of intestinal streptococci.

Bargen, working under Rosenow and with Rosenow's methods, made claims for a "Gram-positive diplococcus" as the cause of this disease. This worker appeared to have dealt with cocci morphologically identical but culturally different. The organisms seemed to be members of the *Streptococcus faecalis* group. Lesions with several distinct or culturally dissimilar streptococci and with mixed cultures were secured from animals. Subsequent experimental work by Paulson showed that various streptococci are found in the lesions of ulcerative colitis; that streptococci indistinguishable culturally from those described in such lesions are isolated as frequently from the distal portion of the normal bowel, and that lesions pathologically identical and similar in location can be produced by several of the streptococci isolated from ulcerative colitis stools as well as by organisms from other sources. Thus, if streptococci bear any relation to the disease, they are significant merely as secondary or contributing factors.

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* There is some evidence that a bacillary dysentery infection may sensitize the bowel so that nonspecific ulcerative colitis develops later.—Editor.

There is no instance on record in which the reported presence of pneumococci has been substantiated by adequate identification.

Deficiency States.—Experimentally, striking chronic lesions microscopically and macroscopically resembling ulcerative colitis in man have been produced in animals by the feeding of vitamin-deficient diets. Recently, Wintrobe, Follis, Alcayaga, Paulson and Humphreys fed a diet deficient in pantothenic acid to a young pig and produced extensive colitis resembling ulcerative colitis in man. Treatment with calcium pantothenate resulted in marked improvement. Unfortunately, at this writing, pantothenic acid deficiency does not seem to be a significant concomitant of human ulcerative colitis, and identical therapy has not proved particularly helpful. Avitaminoses A, B, C, K and possibly D are frequently associated with ulcerative colitis, but have not been established as the prime cause. It is important to realize that, despite an adequate diet, impaired intestinal absorption through hypermotility and involvement of the absorptive areas will lead to a deficiency state. Obviously, inanition or an unbalanced intake will bring about or contribute to such an end. Thus, avitaminoses follow and exaggerate ulcerative colitis.

Alterations or deficiencies in inorganic compound and iron metabolism also are not regarded as of prime etiologic import. When they occur, they, too, are in consequence of the disease and accentuate the problem.

Deficiencies in plasma proteins, clinically evidenced as nutritional edema, and an inversion of the albumin-globulin ratio may also be encountered. These are secondary phenomena.

Psychogenic Influences.—Some authors have expressed the belief that the frequent coincidental relation between emotional upheavals—including those associated with physical trauma—and the onset, recurrence, exacerbation or extension of indeterminate ulcerative colitis is not accidental. The disease is seen in the tense, emotionally unstable and overly sensitive. Sullivan expressed the belief that in as many as 75 per cent of cases the disease is psychogenic. He stated that the process begins as a neurogenic hypermotility, with the small bowel content producing inflammation followed by secondary infection. Emotional immaturity and fearfulness, of the latter of which diarrhea is an expression, were given by Murray as the psychologic characteristics of subjects with this type of disease. I am partial to the psychogenic approach, and some patients have appeared to be helped when treated from this standpoint. On the other hand, proponents of such origin are without controls to establish their theory; and the cautious observer will remember that more persons with identical personalities respond similarly to life's situations without ulcerative colitis than with the disease. Some patients with ulcerative colitis present negligible psychiatric data; few human beings are without any. When patients improve with relatively long psychotherapeusis, the self-limiting propensities of the disease also must be considered. Psychogenic factors, then, are not to be ignored, but they are not the sole causative elements.

Ulcerative colitis may be conceived as a specific reaction to a number of influences which can initate spasm of the colonic musculature. These include possible hyperactivity of the parasympathetic nervous system, infections such as dysentery, and vitamin deficiency. Once the colon becomes spastic, it is potentially an organ that can produce severe damage to its own surface structures. The exhaustion of the secretion of mucus, together with nutritional deficiency, may contribute to prevent healing of the colon.

Lium's work, along with Lium and Porter's findings indicating that colonic ulceration in man occurs where the musculature is the strongest and hence spasm the greatest, is extremely significant. It is in line with my viewpoint of years, that ulcerative colitis is a syndrome in which a variety of factors operate to produce a fairly well defined pathologic and clinical picture. As new factors are discovered, the diagnosis of indeterminate ulcerative colitis becomes narrowed.

Muscle Spasm.—Lium stated, on the basis of experiments:

Focal Infection.—The relation of focal infection remains to be established satisfactorily, both experimentally and clinically. Obviously, all sources of infection should be eradicated when possible, but in no instance could striking amelioration be attributed solely to such elimination. Relief thought to be so obtained often may be purely coincidental because of the self-limiting tendency of the acute phases, or possibly of some influence of other associated forms of therapy.

Blood Cultures.—**Significance With Relation to Etiology.**—Positive blood cultures in the presence of indeterminate ulcerative colitis are of no etiologic significance in view of their rarity, in spite of the ready access to the blood stream of intestinal organisms because of ulceration. When encountered, the organisms were of different types, indicating nonspecificity, and were classified as enterococci. Besides, streptococci not infrequently have been encountered in the blood stream in the later severer stages of a variety of debilitating conditions (Shwartzman).

Viruses.—The evidence to date—experimental and clinical—supports the view that the presence of the virus of lymphogranuloma venereum in intestinal discharge or tissue is of pathogenic significance. Cases in which this virus is present but the clinical picture is indistinguishable from nonspecific ulcerative proctitis or colitis, under which they were heretofore grouped, were first established and can often be separated from those of indeterminate ulcerative colitis by means of bowel antigen (Paulson). This finding has been confirmed by Kirsner, Rodaniche and Palmer, using a somewhat different technic. There is no evidence that any virus is responsible for the colitis in which no pathogenic bacterium or protozoön or virus of lymphogranuloma venereum can be isolated.

Pregnancy.—The evidence to date shows no relation between pregnancy and the onset, recurrence, exacerbation or extension of ulcerative colitis. Such concomitance appears to be coincidental. It appears to occur with rarity, for the problem is encountered infrequently in the Johns Hopkins obstetric clinics; there is a paucity of literature on the subject, and no reference is made to this disease in the standard textbooks on obstetrics.

Allergy.—Andresen and Rowe have incriminated allergy as a cause of ulcerative colitis, basing the theory on the production of acute gastrointestinal allergy in both animals and man (Gray, Harten and Walzer; Livingston; Polland and Stuart), which has given rise to the belief that chronic processes may ensue in some cases. Rowe described the pathologic finding of erythema, inflammation, edema, serous and mucoid secretion and capillary bleeding as characteristic of the allergic process. He expressed the belief that remissions are evidences of transient hyposensitivity or transient failure of shock tissue to react allergenically. Andresen stated that allergy to food—often milk—occasionally is related to the onset and recurrence of the disease. In 44 of 67 cases Mackie showed food sensitivity varying with the severity of the ulcerative colitis. Rowe advanced as further evidence for the theory the purported responses to a soybean dietary elimination routine.

The data are suggestive but not conclusive. The pathologic process in ulcerative colitis, as it is now known, is not pathognomonic of allergy. The differences in food sensitivity in the same patient during several phases of the disease state may be in line with antigenic specificity, which is characteristic of the allergic reaction. However, the inconstancy of the response is not differentiated from the common, purely local phenomenon of undue chemical, thermal and physical stimulation of certain foods, depending on the extent of irritability of affected tissue. The explanation of the remission in ulcerative colitis as due to transient anergy remains to be proved. At best, the Rowe soybean elimination routine produced a response in 7 of 14 cases, which, from a biostatistical standpoint, is not significant. My experiences with this dietary in 7 cases indicate again that so far no one measure will bring about an intermission in this disease. Besides, omission of an apparent food offender (antigen) which is followed by an ability to ingest it without harm is no proof that a desensitization process has occurred. This is not to say that allergy may not be a factor in some persons with ulcerative colitis. While the experimental work in acute gastrointestinal allergy is striking, much remains to be done in elucidation of its relation to ulcerative colitis, and findings in this connection should be interpreted conservatively.

PATHOLOGY

The pathologic picture of ulcerative colitis is one of simple, nonspecific inflammation, the degree of change bearing a relation to the frequency, extent, duration and severity of attacks. The distribution apparently tends to follow a muscular pattern, in that the rectum and tenial bands—the strongest of colonic muscles—are usually affected. Histologically, a picture similar to the acute phase of ulcerative colitis in man has been reproduced in colonic explants of dogs by initiating hypermotility and spasm with Shiga toxin and with prostigmin intravenously and acetylcholine locally. Ulcerations in the colon of lower animals have been produced by vitamin deficiencies. In man, occasionally amebic dysentery—particularly that seen in the living with the rectosigmoidoscope—will resemble ulcerative colitis. The pathologic picture of bacillary dysentery, grossly and microscopically, and many of its sequelae and complications are indistinguishable from those of ulcerative colitis. The thrombotic phenomena in the colon, thought by some to be a feature of ulcerative colitis, are a nondistinctive protective mechanism against gross hemorrhage. They are also seen in bacillary dysentery and in amebic dysentery (Manson-Bahr), as well as in association with gastric ulcerations, but without the marked inflammatory cell invasion of ulcerative colitis and bacillary dysentery. Karsner's and MacCallum's independent descriptions of bacillary dysentery at autopsy showed a striking similarity to those given by others as "characteristic" of ulcerative colitis.

THE CLINICAL PICTURE

Symptoms.—The most common clinical picture encountered on presentation can be characterized as dysentery, constant, periodic or alternated with constipation. A small number of patients have constipation or regular bowel habits, but will have noticed "mucus" or "slime" or small quantities of blood or blood and pus. Malaise and rectal consciousness may be accompaniments. Ultimately, as the condition becomes more intense, the stools become softer, and as the disease extends, there is urgency with greater frequency, resulting in watery stools with blood and pus and increasing weakness, with or without tenesmus. Many patients have abdominal cramps and soreness; a few have tenesmus. Some complain of hemorrhoids, but these are not a common concomitant, especially in the earlier phases. However, complete analysis of the latter complaint sometimes leads to a diagnosis of ulcerative colitis, as it does of cancer. Infrequently, symptoms may arise abruptly, with as many as twenty or more bloody-purulent discharges daily and profound bowel and constitutional manifestations (the acute fulminating type).

Signs.—More than 90 per cent of ulcerative colitis begins at the anorectal margin and involves the rectum and lower part of the sigmoid to a variable degree, more than other segments to which it may extend. Such objective data can be secured by rectosigmoidoscopy. Segments above the lower sigmoid must be examined principally with roentgen rays.

Modes of Onset.—These are of three kinds: (*a*) Acute fulminating: This occurs infrequently and is characterized by an abrupt onset with marked and rapid progression of a severe process with profound toxemia, hemorrhage, hyperpyrexia, tachycardia and prostration. It may be engrafted on a chronic, active process, but rarely. (*b*) Relatively sudden: The onset cannot be dated but is relatively recent. The process is milder than that just noted. (*c*) Insidious: Here symptoms of ulcerative colitis develop gradually, or symptoms of long standing suggesting or in consequence of functional bowel disturbances slowly blend with those of early ulcerative colitis, so that the onset of the disease is not readily determined.

Clinical Forms.—There are two forms, one rarely changing completely to the other:

(*a*) An apparently purely localized process: There are strikingly little weakness, fatigue, loss of weight, abdominal consciousness, anemia or elevation in temperature and pulse rate and an absence of prostration and dehydration, despite active dysentery and colonic involvement. Even the sedimentation rate of red corpuscles, which when elevated can be used by comparative determinations as one of the indexes of the progress of the disease, may be within normal limits. There may be little or no leukocytosis. Extraintestinal complications are not frequent. Incapacity is relatively slight or absent, except possibly in the more active phases. However, such disability is never so pronounced as in the second type.

(*b*) A process accompanied by constitutional manifestations of varying degree: Loss of weight, exhaustion, prostration, pyrexia, tachycardia, dehydration, toxemia, anemia and polymorphonuclear leukocytosis are present. Extraintestinal accompaniments appear here more frequently. Inability to pursue the ordinary tasks is partial or complete.

In this group belongs the infrequent acute fulminating form. It presents all the foregoing signs to a marked degree. The onset is sudden, the process very severe and the progression rapid; as many as twenty or more dysenteric bowel movements occur daily. Hemorrhage is an accompaniment. Cadaver-like appearance, prostration, toxemia, emaciation, dehydration, anemia, pyrexia, tachycardia and leukocytosis occur early and are profound. Heroic therapeutic measures are necessary. Delirium or stupor may be present, and the tendency is toward a rapid downward course. However, some patients survive. If death occurs, it is from exhaustion, cachexia or an intercurrent infection. This phase follows a chronic active, less violent process but rarely.

The Course.—Indeterminate ulcerative colitis is self-limited. The more active phase may run from weeks to months. The disease is characterized by remissions or intermissions, recurrences or exacerbations and progression of varying duration, extent and intensity. These occur at no definite time or stage and cannot be foretold. Eliminating the acute fulminating type, the chronic form tends to be divided into that which presents continuous activity but varying extent and severity and that in which the process abates. However, regression of either type may be relatively slow, although first indications sometimes appear suddenly and without known reason. Reactivation, exacerbation or extension may occur coincidentally with or follow an infection of the upper part of the respiratory tract, psychic and possibly physical trauma, fatigue, excessive or continued nervous tension, bowel abuse by purgation or enemas or dietary indiscretion or appear without any known cause. Recent advances in vitamin, chemical and psychic therapies bring a justifiable hope that the course of this condition may soon be modified and better controlled.

DIAGNOSIS

The diagnosis involves the impossibility of demonstrating any specific agent known to produce the disease. In general, the procedures are those used in ascertaining all prime agents recognized as capable of causing colitis.

The practitioner can employ at least two of them unaided: namely, history taking and physical examination. He should secure others to do as many of the following, in about the order designated, as he himself cannot adequately perform: (1) rectosigmoidoscopy; (2) stool or rectal discharge examinations for determining the presence of gross and occult blood and pus, pathogenic parasites and bacteria; (3) serologic study; (4) gastric analysis, including the use of histamine; (5) the Frei test; (6) the preparation and use of bowel antigen or the injecting of bowel exudate into mouse brain; (7) hematologic study; (8) determination of the basal metabolic rate; (9) roentgen study; (10) elimination diets for food allergy determination; (11) other tests for accessory or secondary chemical deficiencies.

In fact, the proper application of these procedures will solve the diagnostic problems involved in all the diarrheas and dysenteries associated with intrinsic intestinal disease, and most of those concerned with extra-intestinal factors, so far as it is possible in the light of present knowledge.

Measures Used by the Practitioner.—**History Taking.**—In general, this is the most important single measure to be used. It requires tact, patience, time, insight, attention to detail and knowledge of what to attempt to ascertain. A complete history should always be obtained. In the family history, emphasis should be placed on four things: manifestations of allergy, psychoneurosis and psychosis, digestive—particularly intestinal—disorders and neoplasms. The data elicited may point to a hereditary deficiency or tendency.

In the specific history of the diarrhea or dysentery, emphasis should be placed on the following matters:

(*a*) Whether any member of the family, or anyone in the immediate neighborhood is similarly involved: Positive information on this point would suggest amebic or bacillary dysentery, even though either occurs sporadically, as does ulcerative colitis.

(*b*) Residence in tropical or subtropical areas: This question may be important for the possibility not only of the foregoing diseases but of sprue.

(*c*) Food habits: If meat, fish or poultry, a pint of milk, an egg, three vegetables, one of which is carrots or lettuce, and two fruits, one of which is orange or grapefruit, are not ingested daily, there is likely to be a deficiency in essential food elements. This may be an accessory or contributing factor. Food idiosyncrasies or dislikes may suggest allergy.

Recent sources of water and food, as well as occupation, may reveal the pollution of water, contamination of milk or ingestion of poisonous fish or vegetables, infected meat, or nickel, aluminum, copper, arsenic or lead. Lead may be deleterious even when the exposure is to fumes and dust containing it. The so-called paratyphoid group of organisms, certain enterotoxins of staphylococci and streptococci contaminating water or food, may result in an acute gastroenteritis, enterocolitis or colitis which conceivably in certain instances may become chronic.

(*d*) The long-standing administration of enemas, laxatives or purgatives: Such abuse not only disturbs function but, together with lowering bowel resistance, may cause structural change.

(*e*) Veneral disease, particularly when associated with buboes: This should suggest the possibility that the virus of lymphogranuloma venereum is of pathogenic significance in a non-neoplastic bowel disorder with exudation of blood and pus.

(*f*) Psychobiologic aspects: The patient usually is high strung and reacts with excessive sensitivity to his surroundings. Hence, his background and his response to his environment must be ascertained, because of the close relation between their impact and digestive well-being. Significant information is often readily secured by asking several pointed questions, such as "Is the world treating you right?"; "Forgetting your illness for a moment, in what ways have you been disturbed?"; "Are you sad?"; "Do you sleep well?" Close observation of the facial and verbal expressions in response often will suffice or will lead to further questioning. In this way every physician can learn to be his own psychiatrist, reserving psychiatric aid for the complicated problems.

(*g*) Finally, attention to colitis: The time and nature of onset, the character and frequency of defecation, the presence of blood and pus and whether there have been any remissions or intermissions, exacerbations or recurrences are determined. It is necessary also to know whether there have been any constitutional manifestations with previous attacks and symptoms suggesting complications and sequelae.

Physical Examination.—This is rarely of aid or significance. If constitutional manifestations are present, the signs are not unlike those of any severe infection: prostration, dehydration, loss of weight, pyrexia and tachycardia. When complications or extraintestinal manifestations, such as hemorrhage, arthritis, abscess, perforation and carditis are present, the physicial signs indicative of these phenomena will be encountered. In the absence of constitutional manifestations, local or general abdominal tenderness and a spastic anal sphincter, with or without slight elevation in temperature and pulse rate, under-weight, weakness or pallor, may be the only signs encountered.

Other Essential Measures.—Instrumental and laboratory examinations should be undertaken early. If the expectancy of self-limitation does not materialize, the possibility of isolating dysentery bacilli becomes less, since the organisms may be relatively few and tend to disappear shortly after the onset of the complaint.

Rectoscopy, Rectosigmoidoscopy, Bacteriologic and Parasitologic Study.—Rectoscopy is the direct instrumental visualization of the rectum. Rectosigmoidoscopy is the direct visualization of both the rectum and the lower part of the sigmoid. No intestinal study can be regarded as complete when these diagnostic procedures are omitted. More than three-quarters of all intestinal cancers are within 25 centimeters of the anus; in the vast majority of cases ulcerative colitis and amebic and bacillary dysentery affect the rectum and sigmoid. These are within reach of the rectosigmoidoscope. Besides, roentgen study of the rectum and lower sigmoid is inferior to direct visualization. Roentgen study, therefore, should complement rectosigmoidoscopy but should not be used to its exclusion.

The technic is simple. I have used the rectosigmoidoscope on an infant of several hours and on many three weeks old. The procedure is adequately described in books on proctology.

By means of the rectosigmoidoscope, material can be taken directly from the involved distal part of the colon for immediate parasitologic examination. By this measure Paulson and Andrews improved their protozoölogic diagnosis by 350 per cent, as compared with examination of specimens of defecated matter from the same subjects. The immediate inoculation into culture mediums of material secured by this method resulted in more positive cultures of dysentery bacilli than did use of defecated matter. Stained smears of bowel discharge for the tubercle bacillus, its growth on and isolation from artificial mediums and the inoculation of suspected material into guinea pigs with the possible recovery of this organism and study of the nature of the lesion need not be undertaken in the absence of active pulmonary tuberculosis. The reason: Intestinal tuberculosis, when present, usually is secondary to active pulmonary tuberculosis. Incidentally, the available artificial mediums for the cultivation of intestinal parasites are not sufficiently refined for routine use in the clinical laboratory, so that culture cannot supplant the smear method at this time.

Only occasionally does amebic dysentery, with its typical discrete, irregular ulcerations, offer a characteristic rectosigmoidoscopic picture. Bacillary dysentery and ulcerative colitis, and not infrequently amebic dysentery, present indistinguishable appearances.

Serologic Study.—If the diarrhea or dysentery is more than ten days old and neither dysentery organisms nor *E. histolytica* has been isolated, then the patient's serum may be agglutinated against strains of *B. dysenteriae* of Shiga, Flexner, Sonne-Duval and Schmitz types. Complete reliance cannot be placed on the demonstration of blood agglutinins. The only completely satisfactory test is the isolation of the specific bacillus from the feces or from material secured directly from the bowel involvement by means of the rectosigmoidoscope. Only a *strong* serum agglutination response, in a titer of at least 1:300 with the several Flexner strains, 1:200 with the Shiga and 1:200 with the Sonne-Duval organisms,* should suggest infection (it cannot be said to establish it completely.)

Complement fixation for amebiasis has been found by Paulson and Andrews not to be sufficiently refined for routine clinical use and cannot supplant the smear method in the diagnosis of this condition.

Gastric Analysis.—It is essential to know whether free hydrochloric acid is being secreted. Failure to demonstrate its presence might indicate a relation of the problem to a deficiency syndrome. Achlorhydria is not known to bear a direct causative relation to ulcerative colitis.

The Frei Test; Bowel Antigen Reaction; Injection of Bowel Discharge Into Mouse Brain.—The virus of lymphogranuloma venereum may be of pathogenic import in certain types of ulcerative colitis with or without stricture. Sometimes the picture is indistinguishable from indeterminate ulcerative colitis and, no doubt, often has been so designated.

At least, all patients giving a history of venereal disease should be given the Frei test. It consists of the intradermal inoculation of inactivated pus from a bubo due to the virus of lymphogranuloma venereum. A positive reaction indicates a past or present infection—usually secured through coitus—by this agent.

To determine the relation between this veneral infection and a bowel disorder, since a positive Frei reaction in a patient with colitis does not establish such a relation, bowel antigen is made from the grossly feces-free blood and pus from the involved bowel site, obtained through the rectosigmoidoscope, or from the involved tissue.

A positive intradermal reaction to bowel antigen in a person without any active disease or digestive disturbance but with a positive Frei reaction indicates the presence of the virus of lymphogranuloma venereum in the source of the antigen. The present experimental and clinical trends indicate that this is of pathogenic import. Bowel antigens have given this information on occasion when there was no other indication of viral relation to the colitis, even the Frei reaction having been negative (anergy). A negative bowel antigen does not mean the absence of lymphogranuloma venereum.

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* There are other organisms in the dysentery group which may give specific agglutinations and which this author fails to take into consideration.—Editor.

Another means of approach to the same problem has been suggested recently by Rodaniche, Kirsner and Palmer. The suspected bowel discharge is injected into the brain of a mouse. If the virus is present in such material, meningoencephalitis develops in the mouse, and an antigen of its brain tissue produces a positive intradermal response in a person who has been infected with this agent and is known to give a positive Frei reaction.

Hematologic Study.—This is always indicated, to determine the presence of anemia and its nature. The anemia may be primary and a phase of a deficiency syndrome of which the bowel disorder may be a part. The anemia in ulcerative colitis usually is associated with blood loss.

Determination of Basal Metabolic Rate.—Increase in the metabolic rate may indicate hyperthyroidism, which may be totally independent of or contributory to ulcerative colitis.

Roentgen Study.—*Barium enema:* If the diarrhea or dysentery has not subsided within two weeks and the diagnosis is not clear, roentgen examination is indicated, to reach those parts of the colon beyond direct visualization with the rectosigmoidoscope and also the distal part of the ileum. It may determine the character, extent and degree of involvement. Repeated examinations may assist in estimating its progress. Examination with the barium enema is essential in the diagnosis of regional or segmental colitis or distal ileitis.

The *barium meal* should be reserved for studies of the motor activity of the entire intestinal tract and of disorders of the small intestine, including ileitis.

There is no pathognomonic *x*-ray appearance of a specific type of bowel involvement,* save for the filling defect of a neoplasm, the distinctiveness of diverticula, the distention of the small intestine by gas because of obstruction and the *x*-ray appearance of the small intestine in deficiency states, not characteristic of any one type. Thus, occasionally irritable colon may show a picture much like ulcerative colitis, the latter being indistinguishable from bacillary dysentery or from amebic dysentery in rare cases.

Allergic Study.—Allergy should be suspected whenever a reliable family or personal history is obtainable. Its role is best evaluated by elimination diets rather than by skin tests.

Other Tests for Accessory, Contributory or Secondary Chemical Changes.—Deficiency states and electrolyte changes, when present, are thought at this time to be secondary to long-standing debilitating colitis, regardless of cause. Satisfactory quantitative determinations for protein and for the electrolytes calcium, phosphorus chloride, sodium and potassium are available. Little is known concerning changes in the last two elements in the presence of ulcerative colitis.†

Adequate quantitative methods for vitamin determinations have not as yet been developed to a point satisfactory for routine clinical use. As a result, there is still some debate as to the normal vitamin levels in the human being. In the hands of experienced workers, available tests may give dependable results *for comparative purposes.* The determination of the prothrombin time as an index of vitamin K deficiency with hemorrhage has been helpful. Work in the vitamin field is proceeding rapidly, so that much which is said here may soon be in need of revision.

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* The "feathery edge" or "saw-tooth" appearance of the distal part of the bowel is pathognomonic of this type in my experience. Further careful pneumocolon *x*-ray study will often reveal a characteristic appearance.—EDITOR.

† Frequently patients have a *low chloride* level, which may be a factor in the albumin-globulin ratio, the cholesterol level and metabolism and may aggravate this disease.—EDITOR.

Satisfactory tests for the quantitation of blood, lead, arsenic, iron, nickel, copper and aluminum—elements, as noted, which may be factors in acute intestinal processes which may later become chronic—are available. These are highly technical procedures for which the usual clinical laboratory is not equipped. Nevertheless, they give accurate and dependable results in adequately trained hands.

Diagnostic Use of Antidysentery Bacteriophage.—Present methods do not seem sufficiently accurate or refined for clinical use.

Differential Diagnosis.—Ulcerative colitis is differentiated from *amebic dysentery* by the rectosigmoidoscopic demonstration of discrete, irregular, undermined ulcerations with relatively normal intervening mucosa, by the finding of *E. histolytica* in feces or intestinal discharge and by the *complete* subjective and objective relief following amebicidal therapy. These criteria for the diagnosis of amebiasis are important, for about 10 per cent of the population are healthy carriers. Thus, the dysentery may arise in one of them on an entirely different basis. Besides, the role of *E. histolytica* in colitis which responds partially to amebicidal therapy is unsolved. Response to such therapy when this parasite was absent prior to the institution of treatment cannot be used as a therapeutic test for amebic dysentery, for in some cases ulcerative colitis appears to be benefited by such treatment.

Ulcerative colitis is differentiated from *bacillary dysentery* by the isolation of Shiga, Sonne-Duval or Flexner organisms.

The advanced *lymphogranuloma venereum colitis*—that most commonly known—usually is readily distinguished from ulcerative colitis. The former is characterized by a history or evidence of healed buboes or condylomas or elephantiasis of the anogenital region, a rectal stricture with active colitis above it and a positive Frei reaction. However, this so-called typical, advanced state, especially in the absence of condylomas or elephantiasis, may not always be caused by the virus of lymphogranuloma venereum. Not all patients with bowel lymphogranuloma venereum present such extensive involvements. Not all rectal strictures are due to the virus. The less known, earlier, atypical prestricture or nonstricture phases sometimes simulate indeterminate ulcerative colitis. The probable incidence is unknown, since quantitative studies have yet to be made. The Frei antigen alone is inadequate for differential diagnosis, because the patient may give no reaction to it despite indications that the virus is present in the bowel (anergy). Also, a positive Frei reaction may be produced by an antedated or healed virus infection or one unrelated to the bowel disturbance. Bowel antigen, when positive, indicates the presence of this virus in the source of the material from which the antigen was prepared. Such suggested presence, in the light of present knowledge, assists materially in the differential diagnosis. Bowel antigen should be used in the presence of any obscure bowel disorder, particularly when there is a history or an indication of veneral disease.

Differentiation from *mercurial colitis* is by history, pathologic picture and symptoms. There are three types of mercurial colitis: the acute, occurring in cases of suicidal over-dosage of mercuric chloride; the subacute, usually following therapeutic over-dosage as, for example, during treatment for syphilis, and the chronic, in industrial cases. The pathologic picture and symptoms may resemble those of severe ulcerative colitis. There are nephritic changes, and in the subacute and chronic types salivation, sore gums and an ulcerated, edematous tongue are seen. These signs are usually absent in ulcerative colitis.

Uremic colitis is differentiated by its occurrence with acute and chronic urinary disturbances or as a terminal manifestation of uremia, because of the excretion of urea through the intestine.

Thyrotoxicosis is recognized by its usual clinical symptoms and signs, by the elevation of the basal metabolic rate, by diarrhea (not dysentery), by the essentially normal rectosigmoidoscopic picture and by the response to iodine. Thyrotoxicosis and ulcerative colitis may be present concurrently or may be independent of one another, or the former disease may be a contributing factor in the latter.

Carcinoma may be recognized by rectosigmoidoscopic or roentgen examination. The former will demonstrate an ulcerating mass in the rectum or lower part of the sigmoid. Except for the tissue immediately contiguous, there will be no inflammation, edema, ulceration or contraction of the bowel. For involvements above the lower portion of the sigmoid, *x*-ray study is essential; usually it will show a characteristic filling defect.

Intestinal polyps ulcerate eventually, then bleed, and may be associated with frequent bowel movements. They also must be demonstrated by rectosigmoidoscopic and roentgen study, Fischer's double contrast method being used. In true intestinal polyposis the lesions are sessile or pedunculated, have a smooth, rounded outline and are scattered evenly over the whole mucous membrane. The disease is hereditary, transmitted by males and females alike, the inheritance being acquired on a mendelian basis. The polyps secondary to ulcerative colitis are of the irregular shape of the tags of mucous membrane and are usually attached to the line where the bloodvessels pierce the intestinal wall. Neither are to be confused with pseudopolyposis in ulcerative colitis, observed through the rectosigmoidoscope as a bunching together of edematous tissue. With some experience these differentiations are not difficult.

From a practical clinical standpoint, the absence of pulmonary tuberculosis makes remote the probability of *tuberculosis of the intestine,* since primary intestinal tuberculosis is exceedingly rare.

With *regional ileitis—chronic cicatrizing enteritis* (*Crohn's disease*)—diarrhea may be intermittent or continuous, although occult blood will be encountered. The entire clinical picture is milder than that of ulcerative colitis. A normal rectum and sigmoid are seen with the rectosigmoidoscope and a normal large intestine with *x*-rays, except when the process passes beyond the ileocecal valve to involve the proximal part of the colon. With the *x*-ray, a narrowing of the terminal portion of the ileum or mural thickening with consequent stenosis and stiffening and shortening of the involved small intestinal segment with mucosal destruction is noted. Pulmonary tuberculosis is absent, and no tubercle bacilli have been encountered in the lesion. A mass in the lower right quadrant may or may not be present.

Diverticulitis may give rise to blood or blood and pus with frequent bowel movements. The picture, consisting of a localized mass, tenderness, muscular rigidity, nausea, vomiting, pyrexia and leukocytosis, closely resembles appendicitis, but the involvement is on the left side. The rectosigmoidoscope may help in differentiation from ulcerative colitis when the lesion is within reach of the instrument; the rectal and sigmoidal segments will not be diffusely inflamed. The diagnosis is made chiefly by x-ray examination.

Hemorrhoids and foreign bodies, too, will be differentiated readily by rectosigmoidoscopic and x-ray study.

Pellagra and associated proctitis may be differentiated from ulcerative colitis by the clinical picture of cutaneous and gastrointestinal lesions, stomatitis and mental disturbances, which responds to nicotinic acid.

When *hemorrhoids* alone are present, the bowel above them is normal. Foreign bodies are sometimes ingested or are introduced by rectum. In consequence, the mucosa may be lacerated. The history, in addition to data obtained by the procedures I have outlined, will be helpful.

SEQUELAE, COMPLICATIONS, ASSOCIATED LESIONS

One or more of the following may be encountered in the several systems in consequence of ulcerative colitis:

Digestive Tract.—Stomatitis, hemorrhage, atrophy of lingual papillae, glossitis, perforation with the diffuse peritonitis or pericolic, perirectal or perianal abscesses, anal or intestinal fistulas, fissure, stricture, polyps, malignant growths and multiple abscesses of the liver.

Cardiorenal Apparatus.—Carditis and, rarely, nephritis.

Nervous System.—Peripheral neuritis. It may be a manifestation of a toxic condition or of a vitamin B deficiency; the latter condition may be a secondary or a contributing phenomenon with ulcerative colitis. If it responds to thiamin chloride, this complication should be designated as beriberi.

Skeleton.—Muscle inflammation; abscesses; arthritis.

Skin.—Dryness and scaliness; ulceration and abscesses; erythema nodosum; eczema; cheilitis.

Hemopoietic System.—Splenomegaly.

Glandular System.—Inflammation of the parotid gland.

Blood.—A low plasma protein level, low serum calcium, inverted albumin-globulin ratio and sometimes disturbances in the acid-base equilibrium.

PROGNOSIS

It is impossible—statistically—to analyze and correlate the prognostic data available from several sources, because of variations in methods of study and classification. In general, at the present writing, from the experience at the Johns Hopkins Hospital, in only the rarest case is it possible to anticipate permanent freedom from recurrence, exacerbation or extension at unpredictable intervals and of unpredictable duration and intensity.

It appears safe to make several generalizations: The older the subject when first affected, the better the outlook; the longer the history, the lower the mortality; the longer the disease persists, the less the interval and the prospect of intermission—remissions, exacerbations and extensions of varying duration and degree superseding. The severity of the ulcerative colitis and not the extent of the colonic involvement roentgenologically bears a relation to the outcome, duration of activity and estimation of the future course. Complications, such as polyposis, stricture, perianal or perirectal abscess with fistula, arthritis and carcinoma, when present, obviously contribute to the gravity of the prognosis.

TREATMENT

Prevention.—Little is known in this connection, since etiologic factors are not clearly defined.

Psychogenic Considerations.—Since the disease occurs among those who are high strung and tense and who react with excessive sensitivity to their surroundings, prevention must begin in infancy with teaching the mother the importance of calmness and placidity if she does not already possess these. Teaching the child how to get along with his fellows, how to achieve superiority and how to reconcile himself to inferiority and to disappointment, the inculcation of proper habits and good manners, teaching endurance and not permitting discontinuance of a task on the first signs of fatigue are possible in a properly directed discipline in a quiet and intelligent home. To acquire some sense of proportion—readily and constantly to recognize the few major from the multitudinous minor considerations of life—is important. In this way a lesser exhibition of tension in general—and toward many details in particular—becomes possible. It is not impossible to achieve some degree of equanimity and mental repose in subjects in this group. Specifically, and practically, if spasm may be a forerunner of intestinal ulceration, the role of the psychic element in altering intestinal tone cannot be ignored.

The prevention or reduction in frequency of exacerbations, recurrences or extensions, from a psychogenic standpoint, rests on the discovery of the motivation of the complaint and the emotional problems bound up in it. The explanation of pathologic anatomy and pathologic physiology and their possible relations to the associated emotional factors, in simple nontechnical language, often is important. It may relieve fear and anxiety; it may adjust the patient to his disease, and it may indicate clearly to the patient the necessary alterations in attitude, conduct and environment, thereby tending to reduce the frequency and severity of recurrences or exacerbations. The physician should learn to be his own psychiatrist. Complicated problems will call for special psychiatric aid.

Other Factors.—All tensions, strains and fatigue from whatever cause, infections of the upper part of the respiratory tract and ingestion of any food or agent which may have an infective, irritating or laxative influence on the digestive apparatus must be avoided as far as possible. A nap each afternoon aids in relaxation.

Management.—The management of nonspecific or indeterminate ulcerative colitis is primarily medical. Unfortunately, there is no specific therapy available. Therapy to be specific should meet the following criteria: (1) The product used should be prepared from the prime causative organism; such an agent remains to be determined. (2) Adequate employment of any specific measure should result in an abrupt, marked, complete response, without extensions, exacerbations or recurrences; the responses to all or any of the measures now employed are relatively slow, and permanent cessation, save in isolated instances, remains to be accomplished. (3) The attainment of a "cure" should be possible on the use only of the "specific" therapeutic measure; usually multiple procedures must be employed. Certainly it seems fair to say that no single available therapeutic measure will meet these criteria of therapeutic specificity in any stage of ulcerative colitis.

The majority of patients—at least as many as 65 per cent—do comparatively well in the hands of experienced observers using different approaches. Numerous and dissimilar agents have been reported as being helpful. Satisfactory control studies have almost never appeared with therapeutic claims. The spontaneous, natural "curability" of this condition may be as high as the aforementioned figure when the foregoing data are considered along with the tendency of the disease to remit or intermit, with subsequent recurrences, exacerbations or extensions, which again manifest a similar tendency. The remaining severer involvements do poorly regardless of the type of therapy—except in some patients who may respond better to operation. Experiences with the newer chemotherapeutic agents suggest their helpfulness when the disease is milder or not of long standing, and especially during the first attack. Repeated use when the disease recurs is often disappointing, particularly when the same preparation is employed. It is in the light of these facts that the following measures in management are to be considered:

The problem in medical management concerns the proper application of the art of medicine. Often it involves treating the patient first and the disease next. It is directed in great measure toward breaking the vicious bowel habit of hyperirritability and restoring deficiencies resulting from insufficient ingestion, inadequate absorption and the loss of body fluids, which exaggerate the process. As this is being accomplished, the natural reparative forces come into play. The management includes prescribing rest, mental as well as physicial, and a high protein, reduced stimulating (smooth), high vitamin diet, transfusions, intravenous and parenteral use of vitamins, intravenous administration of dextrose and physiologic solution of sodium chloride, sedation and chemotherapy. Vaccine, serum and artificial fever therapy, oxygen administration and rectal instillations and irrigations, in addition to other measures giving symptomatic relief, are also employed.

With acute fulminating ulcerative colitis, the patient should be put to bed and kept absolutely quiet and warm. The loss of body fluids and blood by the bowel is combated by (1) intravenous use of dextrose and physiologic solution of sodium chloride and (2) small, frequent transfusions—200 to 300 cubic centimeters every three or four days. There should be adequate vitamin administration parenterally and intravenously and inunction of vitamins A and D in the form of cod liver oil to insure absorption; this should be done either as a prophylactic measure or for anticipated or evident deficiencies. In this connection, the roles of vitamins C and K in bleeding in ulcerative colitis have as yet not been clearly defined, but the former can be given without harm and the latter should always be administered when there is a delay in the prothrombin clotting time.

To facilitate the formation of new hemoglobin after blood loss, iron in suitable form is essential: ferrous sulfate, 1 Gm. (15 grains), or iron and ammonium citrates, 6 Gm. (90 grains). If either should prove irritating or the dysentery severe, 0.1 to 0.2 Gm. of green iron and ammonium citrates may be injected intramuscularly daily. However, marked local and systemic reactions not infrequently occur.

Deficiencies in calcium and phosphorus are made up by the intravenous and intramuscular use of 10 cubic centimeters of 20 per cent solution of calcium gluconate. The effect may last two hours after intravenous injection, the intramuscular injection prolonging it. This will eliminate low calcium tetany when present, dramatically relax intense muscle spasm and favorably influence colonic hyperirritability. Parathyroid extract and vitamin D are aids in the control of calcium metabolism. Sodium and chloride needs are supplied by parenteral administration of physiologic solution of sodium chloride. Little is known concerning the potassium balance in ulcerative colitis.

Deficiencies of protein and dextrose are treated by transfusions and parenteral administration of dextrose. Protein may be supplied also by giving blood plasma or mixed aminoacids intravenously (Elman and Weiner). It may be given by mouth also when there is reasonable assurance of its absorption.

Frequency of defecation may be reduced with: (1) Suppositories of lead and opium, or opium and belladonna, which may also diminish tenesmus. (2) Small doses of powdered opium or codeine sulfate by mouth from four to eight times daily. The oral dose of each ranges from 0.015 to 0.03 Gm. (¼ to ½ grain), depending on the number of daily doses. These preparations are to be preferred to the tincture of opium, 0.3 to 2 cubic centimeters (5 to 30 minims) several times daily, because of their slower absorption, resulting in a more lasting effect. (3) Finely divided kaolin or barium sulfate, inert substances (4 to 30 Gm. one to four times daily) which are excellent adsorbents and will tend to add bulk and reduce irritability. Either of the last preparations may become an irritant by reason of too great bulk and assume a scybalum-like form if given in excessive quantities.*

Psychotherapy.—This has already been discussed, under "Prevention."

Dietotherapy.—It has been demonstrated experimentally (Alvarez, Hosoi) that foods high in protein leave a minimal residue in the intestine and consequently are negligibly stimulating. Conversely, milk, fruit and vegetables leave relatively large residues and are physically, and fruit and vegetable juices chemically, stimulating. These facts have been applied in a diet formulated by Sister Mary Victor and Bargen.

For the chronic phases, some of the measures used for the acute fulminating type may be employed and found helpful on indication.

For the ambulatory patient with mild involvement, either the relatively high protein, reduced stimulating diet or a smooth (reduced stimulating) diet (Paulson) may be employed at the outset. (Dietary treatment is covered in the chapter by Kate Daum.)

The addition of vitamins should complement either of these diets. There should be three meals daily with either routine; more frequent feedings may mean an undesired increase in peristalic activity.

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* Any drug or drugs which increase the bulk of the stool—particularly bismuth—may produce a pressure necrosis and lead to perforation. I have seen this three times at necropsy. I do not believe this form of medication is advisable.—Editor.

Food Allergy.—Those foods to which the patient has been found allergic on the use of elimination diets are obviously to be omitted from any list. The soybean elimination dietary routine advocated by Rowe may be employed. Its evaluation awaits wider experience. All diets must be well balanced.

Vaccine and Serum Therapy.—Since 1911, vaccines—autogenous and stock, mixed and of a single organism—of intestinal pathogens or nonpathogens, have been reported as giving "good results." If vaccine is to be administered, it may contain about 2,000,000,000 nonviable bacteria per cubic centimeter. Usually 0.1 cubic centimeter is the initial subcutaneous dose. This is increased by a like quantity every third day, if local or constitutional reactions do not ensue, until 1 to 2 cubic centimeters has been given. Frequently this treatment has been continued for two years after symptoms have subsided in the hope of reducing the frequency or severity of recurrences.

Typhoid vaccine has been administered intravenously, apparent benefit sometimes accruing from foreign protein stock.

Serum prepared from horses previously given injections of dysentery bacilli (Hurst), from so-called diplostreptococci (Bargen) or from pooled toxins and vaccines of colon bacilli from normal persons and patients with various disorders (Shwartzman and Winkelstein), as well as ordinary horse serum (Kalk), has been used intravenously and intramuscularly. Favorable claims have been made for all serums. Many competent observers have been unable to duplicate the results reported.

Serum is given intramuscularly as follows: Beginning with 0.1 cubic centimeters, the dose is increased by 0.1 cubic centimeter at eight to twelve hour intervals until 3 cubic centimeters has been given. This is graded up or down, depending on the patient's tolerance. Some may take only 1 cubic centimeter daily and others as much as 5 cubic centimeters.

Serum is given intravenously as follows: 40, 60, 80 and 100 cubic centimeters are injected intravenously on successive days and then 100 cubic centimeters for a few additional days. "The reaction is occasionally somewhat alarming but it is never really dangerous" (Hurst).

Some proponents of vaccine and serum therapy have suggested or inferred specific activity, but the responses, for reasons already noted, are nonspecific and of foreign protein type. No immunity is conferred by these (or any other) measures or, incidentally, by any aspect of the disease itself.

Empiric Measures.—Empirically, such drugs as gentian violet (0.03 Gm., or $\frac{1}{2}$ grain, daily) and tincture of iodine (0.3 to 1 cc., or 5 to 15 minims, daily) are given by mouth. The latter is taken on a full stomach; it is discontinued after two weeks if there is no response attributable to it.

Emetine hydrochloride (with or without an arsenic or oxyquinoline derivative) is sometimes beneficial. In rare instances there is complete subjective and objective relief; when the parasitologic diagnosis has been dependable and *Endamoeba histolytica* not discovered, the result cannot be interpreted as a therapeutic test for amebic dysentery. The intramuscular dose of emetine hydrochloride should never exceed a *total* of 10 mg. per kilogram of body weight.

Liver Extract.—In the hands of Cheney, this has been instrumental in bringing about remissions in 18 of 19 cases, in the majority within the first month of treatment. The follow-up period has been brief. The effect may be due to an unidentified substance in liver extract. Reticulagen (Lilly) is suggested according to the following plan: intramuscular injection of 10 antipernicious anemia units three times weekly for one month, 20 units a week for the second month and 20 units each two weeks thereafter for maintenance.

Artificial Fever Therapy.—Ferguson, Fetter and Schnabel reported the use of artificial fever in 5 cases, with encouraging results. The rectal temperature was raised to 104 to 105 F. in a Kettering cabinet for two to three hours three times weekly. Nothing further appears in the literature concerning this type of therapy.

Oxygen Administration.—Felsen suggested the ultracolonic use of oxygen, but Dack and Dragstedt have found it without benefit. The inhalation of concentrated oxygen in the presence of extreme toxicity has been helpful (Bargen).

Chemotherapy.—Therapeutic responses, despite unpredictability, have been sufficiently encouraging in the hands of some (Collins; Bannick, Brown and Foster; Brown, Herrell and Bargen) in mild and moderate ulcerative colitis to justify the oral use of neoprontosil and the cautious administration of sulfanilamide. The former is less effective but less toxic and is better tolerated than the latter, and therefore appears preferable, particularly because of the necessity of prolonged therapy. In the long run it may be as effective as sulfanilamide. The effect of sulfonamide compounds on ulcerative colitis is unknown. They have practically no bactericidal action *in vitro* on intestinal flora from normal subjects and patients with ulcerative colitis (Paulson). The concentration of sulfanilamide in the blood of those taking adequate doses of neoprontosil averages 2.5 mg. per hundred cubic centimeters. Therefore, the response cannot be explained wholly by the breakdown of neoprontosil to sulfanilamide. The drug may act locally in an obscure manner. Proponents (Brown, Herrell and Bargen) are exceedingly anxious not to create the impression that neoprontosil (and sulfanilamide [Bannick, Brown and Foster]) is a specific remedy for chronic ulcerative colitis.

Dose.—A total of 3.25 to 5.5 Gm. of sulfanilamide or neoprontosil is given at five equally spaced intervals in twenty-four hours for from ten days to two weeks. An interval of one to two weeks with reduced doses (2.5 Gm.) follows. This cycle is repeated several times, or complete rest from the drug for one to two weeks is prescribed, depending on the response. When the condition is resistant, it may be necessary and possible to give neoprontosil continuously for as much as three months with graded doses and without disagreeable effect except for fatigue.

Results.—The untoward manifestations (principally following sulfanilamide), probably on the basis of sensitivity or idiosyncrasy, are: malaise, anorexia, nausea, emesis, vertigo, tinnitus, cyanosis, headache, nervous symptoms, chills and fever. Fatal jaundice has been encountered. Continued use may result in abdominal cramps, increase in diarrhea or dysentery which may call for control by opiates, cutaneous lesions, paresthesia, anemia, leukopenia and granulopenia. The chief difficulty with neoprontosil arises from nausea, sometimes emesis, abdominal cramps and an increase in diarrhea or dysentery. The tendency to recurrence persists, and in suitable cases may make advisable the intermittent use of neoprontosil in graded doses indefinitely. Results of its long use, as well as criteria for a better selection of cases of this type of therapy, are not yet known, but patients to whom these compounds are administered should be warned of their harmful possibilities so they will seek medical aid when symptoms arise; even when without symptoms, they should be observed regularly for objective evidence of such effects.

Sulfanilamide and neoprontosil in my small, uncomplicated series often improved symptoms. Frequently they failed proportionately to influence the healing process, as noted by rectosigmoidoscopy. Whether benefit was coincidental or influenced by the medication could not always be determined, for the cases were relatively few; nowhere were there adequate controls, and healing, partial or complete, may occur without pharmacotherapy. Recurrences, exacerbations and extensions have been seen at varying intervals after the discontinuance of sulfanilamide and neoprontosil, and reinstitution of these drugs has not always been attended by like relief. These experiences in the main have been those also of University of Chicago workers (Dack, Kirsner, Dragstedt and Johnson). However, at this time neoprontosil and sulfanilamide should be continued for whatever benefit may accompany them, because there is not too much else to offer and in order to amass a greater experience in their use.

Succinyl sulfathiazole was shown by Poth and Knotts to exert a marked effect on the coliform organisms of the intestinal tracts of dog and man. A comparable decrease in clostridia also, but not in streptococci, was noted. One to seven days of administration resulted in the *B. coli* count dropping from 10,000,000 to less than 1,000 organisms per gram of wet stool. The relatively odorless feces indicated inhibition of anaerobic proteolytic bacteria too. Of marked importance is the fact that a high concentration of the drug can be maintained in the human gastrointestinal tract, although at the same time, owing to low absorption, the concentration in the blood as free sulfathiazole rarely exceeds 1 mg. per hundred cubic centimeters. The strongly antibacterial action of this preparation appears to be due to the sulfathiazole liberated in the bowel by hydrolysis. The drug has been used for various conditions of the intestinal tract requiring radical operation and in bacillary dysentery. The dose is 0.25 Gm. per kilogram per day, divided into 4 to 6 equal parts. Paulson gave this preparation to 15 patients with ulcerative colitis for from one to two years continuously without any serum bilirubinemia, hematologic alteration or changes in prothrombin time, blood urea and urinary chemical or cellular balance, with two exceptions: In one patient an erythematous rash occurred, and in another, jaundice developed with delayed prothrombin time ascribed to hepatitis. Cessation of administration resulted in spontaneous recovery. In no instance was the free sulfathiazole level in excess of 1 mg. per hundred cubic centimeters of blood. Nevertheless, all patients receiving this preparation should be observed, because occasionally toxic manifestations may develop. Because of its relative innocuousness, this preparation has tended to supplant sulfaguanidine, which produces toxic by-effects frequently and cannot be given over a long period.

The drug is no panacea; there is none. As noted elsewhere, when the disease is in an early, acute stage, without complications, the results are apt to be encouraging. My results are in line with Crohn's: The drug is a useful adjunct in the treatment of ulcerative colitis.

Rectal Instillations.—These have no place when the rectum and lower part of the sigmoid are unaffected. Generally, they are to be avoided so as to put the involved, irritable distal intestinal segments at rest. However, many agents have been suggested, and a few have been said to be helpful; some are harmful.

A Mixture of Kaolin and Aluminum Hydroxide.—Kaolin is inert, acts mechanically by carrying off many bacteria when in motion and adsorbs toxins. Colloidal aluminum hydroxide has similar properties and is added because it has greater colloidal activity, settles out of suspension less readily and is slightly astringent. This mixture was used as follows by Eyerly and Breuhaus:

> The colon was cleansed with a pint of warm water. In an hour this was followed by a retention enema of a 60 to 150 Gm. mixture of kaolin and aluminum hydroxide in 90 to 150 cc. of warm distilled water. This was to be retained as long as there was no discomfort, one or two instillations daily being adequate.

This method appears preferable to oral administration because larger doses can be brought into direct contact with the inflamed mucous membrane, without previous admixture with food and digestive juices. The reaction in the lumen of the bowel is neutral. No implication occurs when moderate care is used. Tenesmus is reduced, and healing may be facilitated.

Sulfanilamide.—This has been recommended for rectal instillation by E. N. Collins. Small amounts are given at the outset, with a gradual increase until the patient retains an instillation of 45 grains of sulfanilamide (powder) in 1 pint of distilled water, warmed to body temperature, twice daily. This treatment may be preceded by use of an opium suppository to facilitate retention. A blood sulfanilamide level of 5 to 7 mg. per hundred cubic centimeters has been maintained in most instances, but the degree of absorption depends on the severity and extent of the disease process.

When this method is used intermittently, hypochromic anemia, Collins stated, is the only toxic effect; therefore, rectal instillation is to be preferred to his original oral route. In the rectal instillation–free interval, iron therapy is given. Eight of 11 patients gave a favorable initial response.

Succinyl Sulfathiazole.—This drug has been instilled rectally, and striking improvement in the rectal involvement has been observed occasionally (Paulson). One hour before instillation, an opium suppository is inserted to reduce peristalsis and to facilitate retention. Then tablets are macerated and suspended in 60 to 90 cubic centimeters of warm tap water. The dose may be as much as 0.25 Gm. per kilogram of body weight, given nightly or every other night.

Azochloramid.—In a comparative study *in vitro* (Paulson) of the bactericidal influences on intestinal flora from normal subjects and patients with ulcerative colitis of neutral acriflavine, potassium permanganate, silver nitrate, tannic acid, sulfanilamide, neoprontosil, sulfapyridine and azochloramid in dilutions used in the bowel, the last preparation proved to be consistently superior. Azochloramid strikingly destroys all types of aerobic and anaerobic intestinal bacteria in high dilutions. It was introduced by Franz C. Schmelkes in 1934. The quantity of chlorine liberated at any one time is smaller than that from any other chlorine compound. As small amounts are gradually released and used in killing bacteria, new quantities are slowly liberated, performing the same action, thus increasing and prolonging its effectiveness. It is relatively nonirritating and, being water soluble and fat soluble, penetrates both aqueous and lipoid phases of tissue. These facts were used in therapy (Paulson) by instituting rectal instillations of azochloramid in a vegetable oil (45 to 90 cc. of a 1:4,000 or 1:2,000 solution) nightly or every other night, to be retained as long as possible. The use of opiates by mouth and of an opium suppository aided retention. Azochloramid—like all other agents—does not cure ulcerative colitis, but at times appears to be helpful. Winkelstein earlier and empirically reached a similar conclusion.

Tannic Acid.—This is an astringent and is still used by some physicians in about a 1 or a 2 per cent solution (a teaspoonful or two in a pint of water) for rectal instillation.

Surgical Measures.—Operation should not be undertaken until all other efforts have proved futile. Intractability to *adequate* medical management is its chief indication. Specifically, surgical intervention is reserved—as for duodenal ulcer—for complications which occur in about 15 per cent of cases. These are: the extensively damaged colon filled with pus and detritus which as a source of absorption leads to severe arthritis, erythema nodosum, pyoderma gangraenosum and other degenerative visceral changes; repeated gross hemorrhages; perforation with or without abscess formation; polyposis with or without malignant change; stricture; fissure; fistula, and hepatica and intraintestinal or peri-intestinal abscesses, including those of the anus.

The exact time in the course of the disease when surgical intervention should be employed is not well defined. Each case is a law unto itself, calling for the exercise of nicety of judgment based on experience. This is partly because of the tendency of the disease to remit and the daily hope of some indication of improvement to spare the patient an ileostomy opening which, in all likelihood, he will have to carry throughout life.

Certain disadvantages follow waiting too long for possible relief from operation. This has resulted in the advocacy by some of earlier operations "before ulcerations have become too deep, the disease very extensive, general resistance lowered and metastatic involvement of other organs and tissues have brought about irreparable damage" (T. R. Brown).

For the acute fulminating type, surgical intervention is questionable. It cannot be expected to stop hemorrhage. The mortality rate is equally high for the medical and the surgical approach. Some patients survive on either form of therapy. Nevertheless, if the indications for operation are severe infection and striking toxemia, then the by-passing of the fecal current by ileostomy is the operation of choice. Sometimes it appears to be a life-saving measure.

For the chronic form affecting the distal colonic segments, intractable to medical management or made so by complications, ileostomy is the procedure of choice, either as a permanent drainage operation or as the first stage of a graded procedure for colectomy. The advantage of an ileostomy is that it puts the colon at rest. It "cures" the patient, in that the dysentery subsides, but rarely cures the disease, because complete arrest of the involvement is not the rule. The disadvantages of an ileostomy are: (1) The mortality rate varies from 22 per cent (Cattrell) to 32 per cent (Rankin). (2) It cannot stop hemorrhage. (3) Closure of the opening is questionable except in rare cases because of exacerbations or extensions. (4) There are great loss of body fluids, disturbance in the inorganic constituents and abdominal skin excoriation from irritating discharge. However, after several months, the ileum becomes larger and hypertrophied and assumes in part the function of the colon; the metabolism becomes normal, and the patient gains weight and strength.

Restoration of bowel continuity following ileostomy should not be undertaken until normal mucosa is seen sigmoidoscopically and until "there is an absence of pus or blood microscopically in centrifugalized salt solution that has been run through the colon from the artificial opening to the anus. When these findings are maintained for two months after stoppage of all irrigation, then it is safe to close the stoma and establish the continuity of the alimentary tract" (Stone's law). In addition, the x-ray (after barium enema) should indicate absence of strictures and give some evidence of distensibility.

Some years ago, T. R. Brown and I advised early ileostomy but rarely had the courage to insist on it, owing to the self-limiting characteristics of the disease and the uncertainty of eventual results. Cattell recently executed this suggestion, hoping to facilitate arrest in a greater number of cases and eventually to restore bowel continuity. Of 9 cases which he reported at varying periods after ileostomy—in 5 of which operation was within six months of onset and after one month of medical management—there were only 2 without recurring activity.

For right-sided colitis including the transverse colon, ileocolostomy or ileosigmoidostomy with subtotal colectomy is the operation of choice. Activity or arrest of the disorder in segments distal to the proposed anastomosis precludes such a procedure. The tissues of segments where the disease has been arrested are vulnerable to reactivation.

In the presence of diffuse polyposis or when the colon does not return to normal or is still a focus of unabated infection with consequent complications despite an ileostomy, colectomy is indicated. There will be a return to usefulness after colectomy when the blood chemical picture, including the mineral metabolism, returns to normal and the ileum assumes in part the function of the large bowel. The mortality rate of colectomy is 20 per cent (Cave), although in Cattrell and Rankin's smaller series the rate was not so high.

Colostomy, cecostomy and appendicostomy are of relatively small use. Either the disease involves the entire colon and the operation is of no value, or, if the colostomy is done above the involvement in the presence of regional colitis, the disease has a tendency to leap over the colostomy site and involve the segments above.

MODE OF DEATH

Death comes in consequence of inanition, emaciation, prostration, toxemia, cachexia, sepsis, complications of the disease and of operative measures and intercurrent infections.

That liver involvement is a possible factor in death has not been substantiated, and clinical evidence of such a relation is rare. Besides, multiple hepatic function tests with severe disease have been negative (Paulson), surprisingly, sufficiently often to justify the statement that "liver death" is infrequent, if not improbable.

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CHAPTER XXXI

"MUCOUS COLITIS" AND "MUCOUS COLIC"

INTRODUCTION

THE secretion of mucus is a function of every mucous membrane. It occurs in response to mechanical and chemical irritation in order to protect the mucous membrane from damage. A large proportion of the cells of the lining epithelium of the colonic mucous membrane, including the crypts of Lieberkühn, are goblet cells, which secrete mucus (Fig. 151). The secretion of mucus is, in fact, the only important secretory function of the colonic mucous membrane. Florey has shown that the sticky mucus secreted by the goblet cells picks up minute particles from the surface of the mucous membrane. Consequently the mucus contains the epithelial débris which is constantly being shed by the mucous membrane and the bacteria which normally inhabit the colon, but their presence, unlike that of leukocytes, red corpuscles or pathogenic organisms, is not an indication of inflammation or infection.

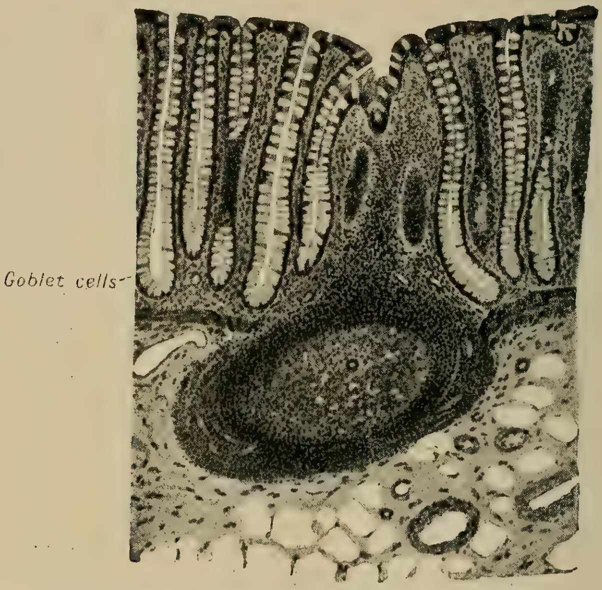

FIG. 151.—Mucous membrane of the human colon, showing numerous goblet cells in the crypts of Lieberkühn (× 70). (After Braus.)

Hard feces in the pelvic colon and rectum act as mechanical irritants and call forth the secretion of mucus, which acts as a lubricant and facilitates their expulsion. As a result of this the dry scybala passed in dyschesia, the common form of constipation resulting from inefficient defecation, are covered with clear mucus, which contains no leukocytes or red corpuscles and no bacteria beyond a small number of the common colon bacilli and enterococci always present in the healthy colon. Endoscopy in such cases reveals a perfectly normal mucous membrane. It is clear therefore that excess of mucus with hard scybala is a normal condition and should never lead to a diagnosis of mucous colitis.

The most common chemical irritants of the colon are purgatives. As they produce purgation by irritating the intestinal mucous membrane, they also call forth an excessive secretion of mucus which contains no leukocytes or red corpuscles, and endoscopy again shows no abnormality in the appearance of the mucous membrane. The mucus protects the mucous membrane so efficiently that actual colitis results only when large doses of strong purgatives have been taken for long periods. Then the diarrhea induced by the purgatives persists when the patient ceases to take them.

Other common causes of chemical irritation are enemas, douches and suppositories. Endoscopic observations immediately after their evacuation show that water and saline solution are the only fluids which cause no irritation. If, however, they are given in excessive quantities—for example, if 20 or 30 pints are run in and out of the bowel in the course of an hour or two, as in a form of intestinal douching which has recently become popular—mucus eventually appears. I have seen numerous patients diagnosed as suffering from mucous colitis who had never passed mucus until douching had brought some away. They had been told that the mucus had been accumulating in the upper reaches of the colon for a long time and was now at last being evacuated, whereas it was in fact secreted as a protest against excessive lavage.

A soap enema results in congestion of the mucous membrane with abundant secretion of mucus containing a small number of polymorphonuclear leukocytes. A turpentine enema produces a still greater reaction, which may be accompanied by small erosions and the appearance of red blood corpuscles as well as leukocytes in the mucus. Glycerin produces an intermediate reaction. The appearance of the mucous membrane and the presence of leukocytes and occasional red corpuscles in the mucus indicate that an acute catarrhal colitis has been produced, but this rarely lasts for more than two or three days. If, however, the treatment is frequently repeated, a true chronic mucous colitis eventually results.

It is clear that the presence of mucus in the stools can be regarded as evidence of inflammation only when it is passed with soft or unformed stools by a patient who is not being treated with aperients or enemas. Even then it may be derived from the small intestine, owing to the presence of enteritis. In such case the stools are watery, and the mucus, which may contain leukocytes and red corpuscles, floats in the fluid; whereas in colitis the stools, though often unformed, are not watery. The fluid material reaching the colon in enteritis may, however, be so irritating that a secondary colitis is produced. Moreover, the irritant which produced the enteritis may have reached the colon in an attenuated form and produced a mild colitis, which then forms one part of an enterocolitis.

When blood or pus or both are passed as well as mucus, ulcerative colitis, or at least hemorrhagic colitis, is likely to be present if carcinoma of the pelvic colon or rectum can be excluded. It is impossible to draw a definite line between "mucous colitis," in which a true catarrhal inflammation of the colonic mucous membrane is present and excess of mucus containing a few leukocytes and perhaps red cells is passed, and the early stages or mildest forms of ulcerative colitis.

Mucous colitis is therefore not a distinct entity and should never be diagnosed. A large majority of persons with a diagnosis of "mucous colitis" are constipated patients passing mucus with scybala or passing loose stools as a result of taking purgatives. Others have gastrogenous diarrhea or eneritis. A minority have carcinoma of the colon or a true colitis, which cannot be clearly differentiated from ulcerative colitis.

There remains the condition formerly known as mucomembranous colitis, in which excess of mucus in the form of thin membranes is passed. This is not a true colitis at all and is best called mucomembranous or mucous colic, as Ewald was the first to suggest. This condition requires separate consideration.

MUCOUS COLIC

Definition.—Mucous colic is a functional condition of the colon, which manifests itself by excessive and incoördinate motor activity and excessive secretion of mucus.

Etiology.—Until 1914 mucous colic was a common disorder among high-strung women between the ages of twenty and fifty, but the severe form is now very rare, and even mild disease is much less often seen than formerly. This is in spite of the fact that colon spasm, with which it is always associated, is as common as ever. Mucous colic has always been rare in men, and its incidence is much higher among the well to do.

Pathogenesis.—Though still often referred to as mucous or mucomembranous colitis, the word colitis is incorrect, as the condition is purely functional. The mucus excreted with the stools does not contain any leukocytes or red corpuscles; endoscopy reveals a perfectly healthy mucous membrane, and the stools and mucus contain no pathogenic organisms.

The colon has a double nerve supply—the sympathetic, stimulation of which leads to inhibition of movement and reduction of tone, and the parasympathetic, stimulation of which leads to increased motor activity and tone and increased secretion of mucus. In mucous colic the normal balance between the sympathetic and the parasympathetic nerve supply is upset; the resulting parasympathetic over-activity causes incoördinated muscular action, in the form of irregular spasmodic contractions of the colon and excessive secretion of mucus. As the former interfere with the normal evacuation of the bowel, the mucus is retained *in situ* sufficiently long to coagulate. It is consequently passed in thin membranous shreds, which may be of considerable size and form complete tubular casts of a segment of the colon several inches in length.

Mucous colic is sometimes regarded as the colonic equivalent of asthma, but there is no evidence that true mucous colic is ever a result of allergy. It is never associated with asthma; eosinophilia is never present, and eosinophil cells are not found in the mucus. There is, however, an allergic condition affecting the colon which may properly be regarded as a kind of abdominal asthma, but although mucous casts are occasionally passed, this is clinically distinct from what is generally known as mucous or mucomembranous colic.

Symptoms.—The patient complains of pain in the lower part of the abdomen, especially over the cecum and ascending colon on the right side and the descending and iliac colon on the left. The pain is intermittent and tends to occur in attacks of a few days' duration. It is often worst immediately after meals and after defecation.

The patient is always constipated, and the feces are hard and dry unless aperients have been taken. Mucus may be passed with or apart from the feces; it is always in the form of membranous shreds, which may be mistaken by the patient for tapeworms or intestinal mucous membrane. Blood and pus are never present. Intestinal sand, which consists of insoluble calcium soaps of palmitic and stearic acids with an equal quantity of calcium phosphate, is often present in the stools.

The whole colon is palpable with unusual ease; it is often possible to feel the cecum and ascending colon and the iliac colon alternately contracting and relaxing in the course of the examination. Anal spasm is frequently found on rectal examination, and alternating contraction and relaxation can sometimes be seen on endoscopy.

The patient is always of a nervous temperament and often shows a morbid interest in the character of her stools. The general health is often unimpaired, but in severe involvement anorexia may develop and the patient becomes wasted, anemic and weak.

Prognosis.—Mucous colic may persist for years without causing more than occasional discomfort. On the other hand, it may absorb so much of the patient's interest that she becomes progressively more hypochrondriacal till she has no interest in life beyond her symptoms, and she may even become bedridden. These variations depend on the patient's mental attitude rather than on the severity of the physical disorder. Complete recovery may take place at any time; this is generally the result of treatment and is rarely spontaneous. There are no complications, and mucous colic is never fatal.

Diagnosis.—Though the clinical picture and the stools are characteristic, it is important to exclude organic disease, especially carcinoma of the colon, in which membranous shreds of mucus are occasionally passed, especially in women who have long suffered from chronic constipation. The presence of even a trace of blood or pus in the stools should throw doubt on the diagnosis. In case of doubt an x-ray examination should be made after an opaque enema; the mucus should be examined for leukocytes, red corpuscles and pathogenic bacteria, and sigmoidoscopy done.

It is necessary also to distinguish ordinary mucous colic from attacks of abdominal allergy, in which mucous casts are sometimes passed. In the latter condition diarrhea is as common as constipation, whereas in untreated mucous colic constipation is always present; further, in the allergic disorder the mucous contains large numbers of eosinophil cells and occasionally blood, neither of which is ever found with ordinary mucous colic.

Treatment.—The underlying nervous state requires first consideration. The conditions in the patient's home are generally unsatisfactory, and it may prove difficult to put matters right. A young woman with mucous colic is often the sole interest in life of her widowed mother, who requires treatment as much as her daughter if the latter is to be saved from chronic invalidism. Alternatively a mother may make her own mucous colitis an excuse for tying her daughter to her side and preventing her from living her own life. The patient should be encouraged to find some congenial occupation and to take an adequate amount of exercise. Bed is the worst place for a patient with mucous colic except during attacks of unusual severity. In many cases a course of psychotherapy does more good than any local treatment, as mucous colic is often nothing more than the physical expression of an anxiety neurosis.

The irritability of the visceral nervous system can be reduced with small doses of bromide, and the tendency to spasm can often be controlled with belladonna. A mixture containing 5 grains of sodium bromide and 5 to 10 minims of tincture of belladonna given three times a day after meals is often useful, and the insomnia which may be present should be treated with phenobarbital or soluble barbital.

The treatment of the constipation in mucous colic does not differ from the treatment of uncomplicated constipation. It is, as always, of great importance to avoid irritating aperients, which increase the tendency to spasm and greatly aggravate the pain. Fruit should be given with each meal, and green vegetables in the form of purées with lunch and dinner. The stools should be rendered soft and more bulky and therefore more easy to expel with liquid paraffin and unirritating vegetable mucilages. If the bowels still do not act satisfactorily, 6 ounces of liquid paraffin should be run into the rectum on going to bed and retained during the night. Liquid paraffin is more effective than olive oil for this purpose and generally results in the bowels being well opened the following morning. In some cases a teaspoonful of castor oil given every evening has an excellent effect, although the dose is insufficient to act as an irritant to the bowel.

Lavage of all kinds is best avoided; the double douche which originated in Plombières certainly produced more mucous colic than it ever cured, and the modern method of washing the colon out continuously for an hour or two with 20 or 30 pints of water is most pernicious in its effect on the patient's mind as well as on his colon. The use of antiseptics, such as potassium permanganate, is irrational, as the only bacteria present are harmless, and the antiseptics are unlikely to destroy even these organisms unless introduced in sufficient concentration to damage the mucous membrane. In exceptional cases, in which scybala are retained in the colon in spite of the use of liquid paraffin enemas, it may be necessary to wash the colon out under low pressure with 1½ pints of warm water once a week through a catheter introduced not more than 2 inches beyond the anus.

Spa treatment is generally undesirable, as the waters of such places as Harrogate, Bath, Plombières and Chatel-Guyon, whether introduced *per os* or *per anum*, have no specific effect, and the intestinal symposiums in the public rooms of the hotels are likely to aggravate the hypochondriacal tendency already present. A holiday in the country, especially in the mountains, where the patient is encouraged to lead a normal life and to forget her abdomen, is, however, often extremely beneficial, especially if she leaves her anxious relatives at home.

It is scarcely necessary to add that all the operations which have in the past been performed for patients suffering from mucous colic do much more harm than good. Few patients escape appendectomy, but operations for dividing adhesions and colopexies for producing them, short circuiting and colectomy are survivals of the darkest age of abdominal surgery.

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CHAPTER XXXII

DIVERTICULOSIS AND DIVERTICULITIS

While there is no reason to presume that the actual incidence of diverticulosis and subsequent diverticulitis has increased, the number of proved cases is much greater each year. A marked improvement in diagnostic methods, including the better understanding of the use of the sigmoidoscope and the more frequent application of contrast *x*-ray technic, is unquestionably responsible for the larger number of persons in whom the lesions are now demonstrated.

Because of the opportunity thus afforded for observation of the course and sequelae in a large number of cases, there has come about a considerable improvement in management, including differentiation between cases in which medical treatment is satisfactory and those in which operation is imperative. Moreover, it is no longer pardonable to subject patients with obstruction due to diverticulitis to hazardous one stage resections of the portion of the colon involved on the presumption that the lesion might be malignant and that the differential diagnosis should be made only by examination of the excised specimen.

INCIDENCE

Only during comparatively recent years have sufficiently large series of consecutive cases been studied to establish a reliable figure for the incidence of diverticulosis and diverticulitis. Contributing also to the accuracy of the estimates has been the increased use of *x*-ray and sigmoidoscopic examinations.

Rankin and Brown estimated the incidence of diverticula in the general population as less than 1 per cent. Since the condition is found essentially during the middle and later decades of life, the figures quoted by Mayo as to the incidence among 26,699 persons who had *x*-ray studies made of the colon (5.89 per cent), and among persons over forty who came to autopsy (slightly more than 5 per cent), are more significant. Spriggs found that 10 per cent of 3,208 patients who were studied radioscopically with barium had diverticula. For the number of cases in which diverticulosis ultimately progresses to diverticulitis, the figure quoted by most authors lies between one-fourth and one-fifth, although a recent study made by Brown and Marcley indicated a lower ratio.

Diverticulum formation in the colon rarely occurs in very young persons. Finney reported the condition in a child of three years, and isolated instances during the second and third decades account for a very small percentage of the total number of cases. During and after the fifth decade probably 95 per cent of lesions occur, with the average age in the neighborhood of fifty-five or fifty-six. The average age appears to be, as one might suspect, a few years higher for diverticulitis than for diverticulosis.

Our own observations tend to bear out the common conception that a tendency to corpulence and sedentary habits is characteristic, although Mayo stated that in 1,500 cases the percentages of under-weight and overweight patients with diverticulosis were about the same.

In a large number of cases there was a ratio of about one and one-half or two males to one female, but Ochsner and Bargen found diverticulosis almost equally divided between the two sexes and diverticulitis, particularly its complications, more common in males.

ETIOLOGY

The most frequently mentioned explanation of the cause of diverticulum formation is usually credited to Klebs, who in 1869 directed attention to the relation of diverticula to the point in the bowel wall at which the bloodvessels traverse it and noted that many sections of the bowel containing diverticula have a short mesentery and that the dragging effect of the bloodvessels supplying that portion of the bowel may produce diverticula. Spriggs subscribed to the theory that diverticula are related to the points where bloodvessels pierce the bowel wall, but stated that diverticulum formation was proceeded by some pathologic change in the bowel wall. Lockhart-Mummery took issue with Spriggs' latter statement, expressing the belief that the mucosa herniates where the bloodvessels pierce the walls of the bowel and that this is the initial process. He admitted the possibility

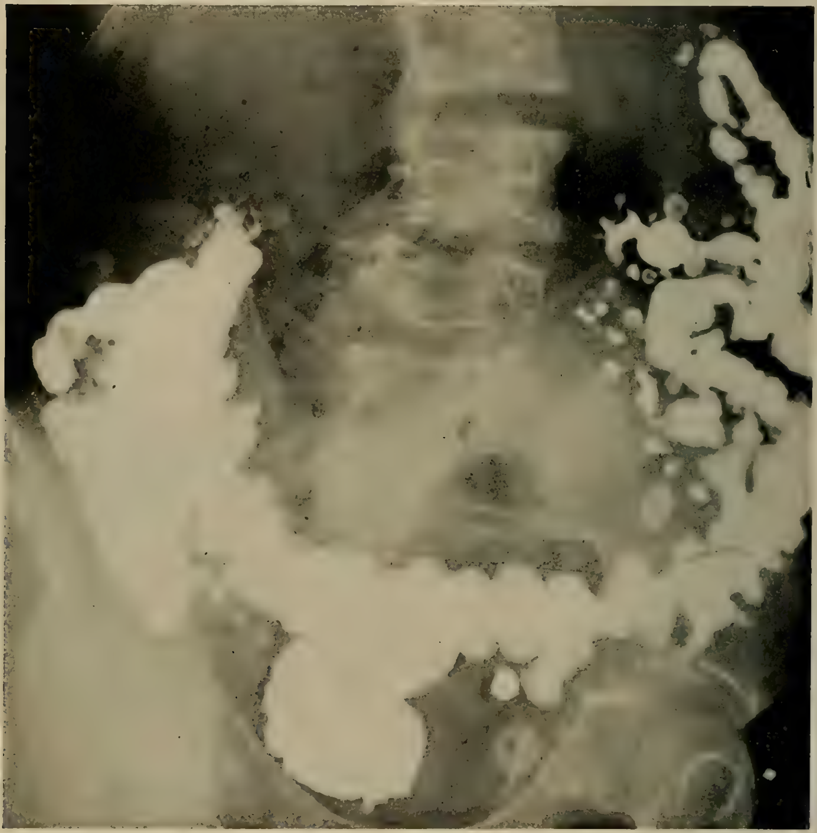

Fig. 152.—Roentgenogram made after the giving of barium, showing multiple diverticula scattered diffusely throughout the colon.

that some degenerative change of the bowel wall allows the herniation to occur, but stated the opinion that any inflammatory change is secondary.

While this theory is plausible and possible, it does not explain altogether the physicial force that initiates diverticula. Most observers look on them as pulsion diverticula, therefore, formed by or as a result of an increased pressure within the lumen of the bowel. Since pressure is present within all colons, some relation would have to exist between its intensity and the inherent resisting power of the bowel wall. Experiments purporting to demonstrate this effect on postmortem specimens of bowel are frequently disqualified on the ground that the bowel after death would probably not react in the same manner as the bowel in the living subject.

There is little evidence of the strictly congenital origin of these diverticula, but that some inherited predisposition to a generally weakened musculature exists would be hard to disprove. Evidence of their true congenital origin is usually discounted on the ground that the muscular layers are either greatly attenuated or completely lacking, while true diverticula, which are thought to be congenital and of which Meckel's diverticulum is an example, most frequently contain all the layers of the bowel wall in their proper proportions.

Telling and Gruner expressed the belief that it is impossible to dissociate the frequent involvement of the sigmoid flexure by diverticula from the physiologic role of that structure. Certainly this feature has to be given credence, yet histologically no great difference can be found between the structure of the sigmoid and that of other parts of the colon.

PATHOLOGY

Diverticula of the large bowel may occur in any portion of the colon. They may occur singly or in very large numbers diffusely throughout its entire length. They are rarely found in the rectum, and the sigmoid alone or the sigmoid and the descending colon are more frequently involved than all other parts of the gastrointestinal tract below the stomach combined, accounting together for 75 to 80 per cent of colonic diverticula, with the sigmoid alone accounting for the vast majority of these.

In the small intestine diverticula are in the mesenteric attachment, whereas in the colon they may occur anywhere around the wall of the bowel except between the layers of the mesentery and through the taenia. They are not confined entirely to the antimesenteric surface, but are frequently found extending into the appendices epiploicae.

Either the diverticulum begins as a hernial out-pouching of the mucosal layer of the colon through the muscular layer, or one or both of the muscular layers may be pushed ahead of it. Externally it is covered by the serosal layer of the bowel. The herniations vary in size from microscopic to larger than 1 centimeter in diameter. There is a tendency for the sac to become larger, with a consequent thinning of the wall, particularly noticeable in the muscular layers. In the larger diverticula the outer longitudinal muscular layer is frequently very thin or absent. The circular layer may be greatly attenuated; the muscle bundles may be separated and the structure deficient, or this layer likewise may be absent, with only the mucosal and serosal layers of the bowel comprising the wall of the sac. The diverticulum tends to be flask shaped, with the neck and opening into the lumen of the bowel much smaller than the diameter of the sac itself. This creates a mechanical deterrent to expulsion of fecal material which enters the sac. Consequently, fecaliths remain over long periods, with resultant damage to the mucosa lining the wall of the sac and possible impairment, by constant irritation, of the blood supply to the sac wall.

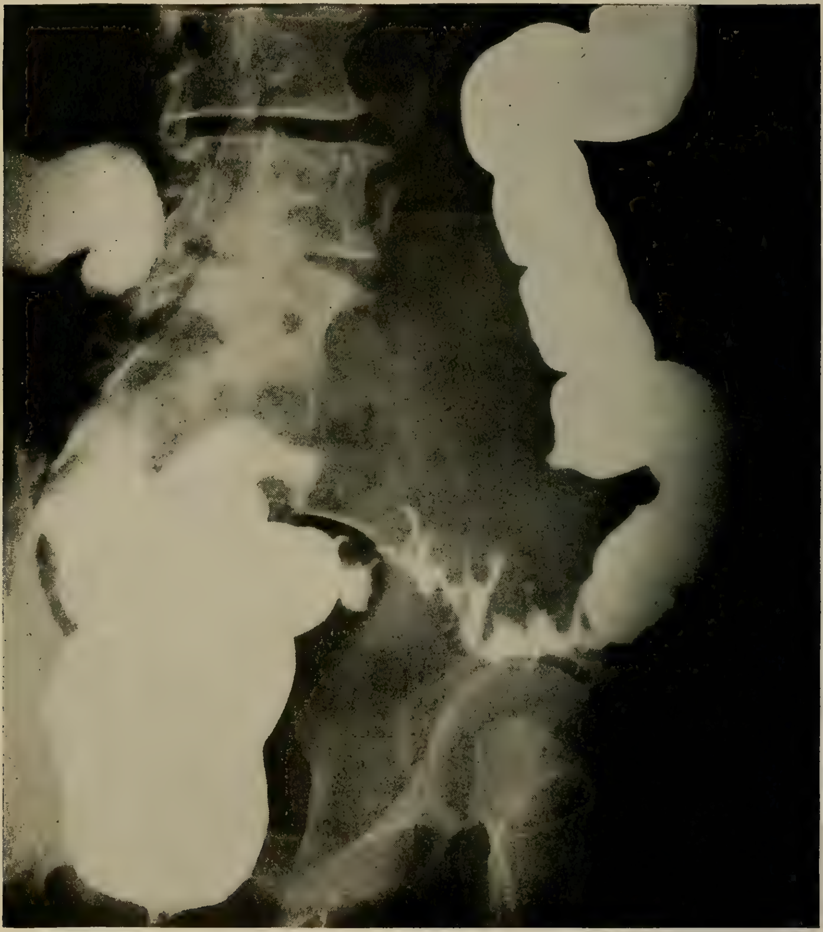

Fig. 153.—Roentgenogram made after the giving of barium, showing the sigmoid flexure involved by diverticulitis.

Obviously the most likely complication of a solitary diverticulum is inflammation of the wall with resultant peritonitis. Sudden perforation, explainable on this basis, occurs usually while the patient is straining at stool or as a result of any sudden trauma. Of course frank perforation is not necessary to the setting up of a local inflammatory process involving the peritoneum surrounding the diverticulum, any more than it is to the inception of an inflammatory reaction about the appendix. The virulence of the infectious process may be slight, yet with the thin wall of the sac, the edema and the possible impaired blood supply, an acute gangrenous inflammation leading to a localized or generalized peritonitis may result, or the process may run a chronic course with latent acute exacerbations. The process may involve one or more diverticula individually.

In the sigmoid, concomitant reaction of the adjacent bowel wall is very likely to occur: As a result of the chronic low grade inflammatory process, a marked hyperplastic reaction forms and may completely surround the bowel through several inches of its length. This process in the sigmoid, by common usage, has come to be designated clinically by the unqualified term diverticulitis. It causes the bowel wall to become markedly thickened and constricted, with resultant narrowing of the lumen of the bowel and, together with the possible inflammatory reaction in the fat of the appendices epiploicae, accounts for the frequent tumefaction. Observers agree that this hyperplastic fibrous tissue reaction results from the escape of bacteria and their toxins, requiring probably a relatively long period. Wilson in 1911 described this process and applied to it the term peridiverticulitis. His explanation was that owing to the thinness of the walls of the diverticula the bacterial contents of the colon escape into the subserosal layer of the bowel without actual rupture of the mucosal or submucosal layers. He observed some instances, particularly when the opening of the

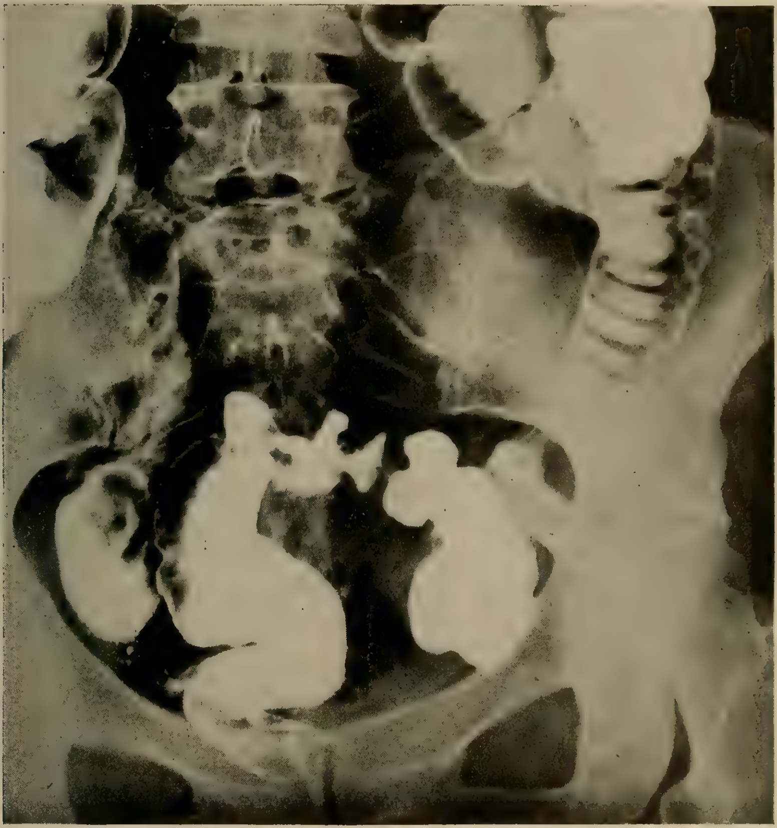

Fig. 154.—Roentgenogram made after the giving of barium, showing carcinoma in the sigmoid flexure.

diverticulum into the bowel lumen was patent, in which no inflammatory changes had taken place in the mucosal epithelium lining the diverticulum. Diffuse infiltration of the subserosal tissue with leukocytes and in some instances a marked increase in fibrous tissue were observed.

RELATION OF DIVERTICULITIS TO CANCER

No reliable evidence supports the view that the relation between diverticulitis and carcinoma of the colon is more than incidental, although the clinical pictures may be very confusing and often impossible to differentiate by physical examination alone. Undoubtedly before sigmoidoscopic and roentgen examinations were available the conditions were confused in many cases, even at the time of surgical exploration, probably accounting for many reports of so-called spontaneous cure of cancer of the colon.

There is no reason why a colon which is the site of diverticulum formation, either with or without a coëxisting diverticulitis, may not also give origin to a carcinoma. Relatively few cases of double involvement have been reported; but little search is made in resected carcinomas for diverticula (Telling and Gruner), and identification requires very delicate examination of the fresh specimen. Wilson in 1911 found 4 carcinomas in association with diverticula of the colon among 15 specimens and expressed the opinion that possibly the association was more intimate than had formerly been thought.

SYMPTOMS

It is commonly agreed that diverticulosis is asymptomatic and that only with some degree of diverticulitis are symptoms produced.

In a study of 72 ambulant patients with diverticulosis, Willard and Bockus found that well over 50 per cent had symptoms which they interpreted as due to this condition. Generally the symptoms are those frequently ascribed to an "irritable" or "unstable" colon, such as intermittent diarrhea, constipation, epigastric pain or distress, flatulence and lower and general abdominal pain. Moreover, while purely clinical and radiographic evidence may show only a diverticulosis, it would be difficult to show that the symptoms did not arise from at least a mild degree of inflammation of the diverticula which had not progressed to the classic hyperplastic process referred to by Wilson as peridiverticulitis.

Pain is the foremost and most constant symptom. However, no particular characteristic of this pain can be considered typical. It is usually located in the left lower quadrant of the abdomen and is of the type usually associated with some degree of obstruction to the lumen of the bowel. Frequently it is intermittent, lasting for several days or a few weeks, and is commonly described as cramping or "due to gas." Frequently expelling gas by rectum may relieve pain. Its severity is variable, depending on the acuteness and extent of the inflammatory process and the degree of obstruction, which, while in some cases rather extreme, seldom is so nearly complete as that frequently seen when a carcinoma involves the left side of the colon. With proper management, an attack frequently subsides, and the patient resumes a rather normal bowel routine. The attacks are frequently accompanied by a low grade fever, some elevation of the leukocyte count, gaseous distention of the abdomen, nausea and, commonly, symptoms referable to the bladder, such as frequency and dysuria. Also frequently associated is some alteration in the normal bowel habit. This is somewhat inconstant as to type—possibly, and perhaps usually, being a tendency toward constipation, while commonly seen also are attacks of diarrhea or alternating constipation and diarrhea.

A palpable mass is felt in perhaps half the cases. This mass is not constant, however, and may either materially diminish or disappear entirely when the exacerbation subsides.

The passage of blood by rectum, when associated with either known diverticulosis or suspected diverticulitis, demands immediate and often intensive investigation. Theoretically, at least, only in diverticulitis should the mucous membrane become ulcerated; yet not infrequently we see persons for whom the only plausible explanation for either massive solitary hemorrhage or the continued presence of small amounts of blood in the stool is diverticulosis apparently without inflammation. Because bleeding from internal hemorrhoids is frequent, it is difficult and sometimes impossible to evaluate its importance when associated with symptoms referable to the colon. But in the presence of a mass in the sigmoid flexure, frequent in both diverticulitis and carcinoma, it becomes imperative to know that the source of associated bleeding, more common with carcinoma, is not the bowel. Of course bleeding can occur from both the bowel and the rectal mucous membrane.

In the main, the characteristic symptoms and findings aforementioned are associated with the clinical type classified by Mayo as self-limiting diverticulitis and peridiverticulitis and follows the pathologic features described by Wilson under the latter term.

Symptoms may vary from this general pattern, usually as a result of complications either following in the wake of the peridiverticulitis or associated with an inflammatory rupture of a single diverticulum, even in the absence of an extensive fibrous tissue reaction in the wall of the bowel. In persons past middle life, localized abscesses in the left lower quadrant of the abdomen frequently are the result of rupture of a diverticulum, or perhaps, as some authors have contended, the thinness of the wall of the diverticulum allows sufficient bacteria and toxins to escape without actual perforation to produce a localized or spreading peritonitis. Although inflammatory processes resulting from the rupture of a solitary diverticulum are commonly confined to the left side of the abdomen, this is not always the case, as demonstrated in a recent review by Baker and Carlile. In 37 cases recorded in the British and American literature of the past twenty years and 2 cases of their own, inflammatory lesions had developed in the right lower quadrant about a solitary diverticulum of the cecum. Generally speaking, however, perforation of a solitary diverticulum in a mobile portion of the bowel is uncommon.

Another and perhaps the most common complication of diverticulitis (*i. e.*, peridiverticulitis in the sigmoid) is secondary involvement of the urinary bladder. Bladder symptoms are complained of by perhaps a fourth or a fifth of patients with diverticulitis. The simplest manifestation results from extravesical irritation produced by the inflammatory pelvic mass, causing frequency of urination and dysuria. It is not unusual to find the bowel adherent to the bladder with rather dense adhesions, and a subsequent fistulous communication between the bowel and the bladder is perhaps the most common serious complication. A history of passage of fecal material mixed with the urine or of gas by way of the urethra is of course pathognomonic of a fistulous communication between the bladder and the bowel; and the usual cause is either diverticulitis or cancer of the pelvic colon, with diverticulitis accounting for it in the majority of cases.

A fistulous communication may be established also between the sigmoid flexure and other portions of the bowel or to the outside through the skin. We recall 2 instances in which perirectal sinuses led to a low-lying ruptured diverticulum. In exceptional cases these tracts may be multiple and involve several structures, which naturally increases their seriousness.

Some rare complications have been recorded in the literature. Whyte in 1906 and several later writers reported abscesses of the liver, both single and multiple, from mesosigmoid abscess complicating and connected with diverticula in the sigmoid flexure. Still more rare were the observations of Eichbaum, of general "sepsis from a phlegmonic diverticulitis of the sigmoid," and of Foggie, who at postmortem examination of a patient treated for cerebral hemorrhage found embolic abscess in the brain as well as in the lungs from multiple suppurating sigmoid diverticula.

DIAGNOSIS

Accuracy in the preoperative diagnosis of diverticulosis and diverticulitis, as of many other diseases, has run closely parallel to the development of methods of study supplementary to the clinical history and physical examination. However, no implication that these are outmoded or unimportant is intended. The clinical history alone is all important, particularly for diverticulitis, and if carefully elicited will, in most instances, lead one to the correct diagnosis. However, the frequent question whether a given lesion in the sigmoid flexure is diverticulitis or cancer makes it imperative that these adjunct methods, namely, roentgen examination of the colon and sigmoidoscopy, be used.

No physical sign can be elicited in cases of diverticulosis. When, however, diverticulitis is present, some degree of tenderness in the left lower quadrant is usually found. This varies with the acuteness and the extent of the process. A mass is always present when diverticulitis and peridiverticulitis have progressed to the stage of obstructive symptoms. This mass is palpable, depending largely on the stature and the thickness of the abdominal wall, in perhaps a third to a half of the patients.

Accurate diagnosis can be established only by the demonstration of the diverticula, chiefly by roentgen examination of the colon by means of the barium enema. Administration of the opaque medium in this manner rather than by mouth prevents additional intestinal stasis above the lesion, and, of course, the element of time to allow the barium to reach the colon does not have to be reckoned with. Uncomplicated diverticula are filled with the opaque medium and appear on the film usually as rounded out-pouchings in relief along the border of the bowel.

Fluoroscopically, diverticulitis is manifested by varying degrees of spasm and hypermotility of the segment involved, usually the sigmoid flexure, together with varying degrees of obstruction due to the narrowing of the lumen of the bowel by the fibroplastic reaction or by the spasm.

Either or both of these may be sufficiently marked to reduce greatly the caliber of or, for the time being, completely to obstruct the lumen of the bowel.

In contrast to carcinoma, the segment of bowel involved by diverticulitis is usually longer; and while there is a sharp demarcation between cancerous and normal bowel, diverticulitis does not terminate abruptly but becomes, as it merges into the normal contour of the bowel, fusiform or spindle shaped.

Relative to the diagnosis of diverticulosis and diverticulitis, the statement is often made that sigmoidoscopy is of little value. This is not true. Within fairly recent years it has been found that, while in no way does it approach the usefulness of *x*-ray examination, it should be carried out in addition to, and preferably before, roentgen study of the colon. Several sigmoidoscopic signs are remarkably reliable for the diagnosis of diverticulitis. True, all of them are not observed in all cases, but, conversely, encountering one or more of these signs during a routine sigmoidoscopic examination will frequently lead one to the diagnosis of unsuspected diverticulosis or diverticulitis.

These signs have been adequately described by Buie, substantially as follows: The only pathognomonic evidence of diverticulum formation, so far as sigmoidoscopy is concerned, is the visualization of the opening of one or more of them during an examination. (That this is more than an occasional accidental finding is doubted by many competent observers, but we have seen it on numerous occasions during routine sigmoidoscopic examination.) There is often fecal material engaged in the opening. Interpreted accurately, sacculation of the sigmoid flexure gives one a strong suspicion of the presence of diverticula. Sacculations occur as shallow out-pouchings of the wall of the bowel, separated by folds or ridges of mucosa which do not disappear as the sigmoidoscope is advanced. When they are definite, roentgen examination of the colon will reveal diverticula in a very large proportion of cases. These sacculations, along with visible openings of diverticula in the bowel, are likely to be found when no peridiverticulitis or perisigmoidal inflammatory reaction is present.

Other signs, more likely to be observed when an inflammatory process is present and suggestive of diverticulitis if no malignant process is encountered, are: a relative degree of fixation of the sigmoid flexure, mucosal edema, marked angulation of the bowel, around which one may not be able to pass the sigmoidoscope, and a reduction in the size of the lumen of the bowel. In a recent statistical study Jackman and Buie found that sigmoidoscopic examination revealed or gave some evidence of diverticula in two-thirds of the patients in which they existed.

In the diagnosis of diverticula of the colon, sigmoidoscopy is not advocated as competitive with roentgen study of the colon. Rather, it should be a routine procedure for any patient presenting a history of possible colonic or rectal disease. By its use the clue to the diagnosis of diverticulosis and diverticulitis will frequently be found, and the differential diagnosis between carcinoma and diverticulitis of the sigmoid flexure will often be simplified. Further, when a surgical procedure is contemplated it is the most accurate means available of ascertaining the amount of normal bowel existing distal to the lesion.

TREATMENT

Rational treatment of diverticulitis must be considered from both medical and surgical standpoints. The present day opinion regarding the indications for surgical interference is more conservative than that of at least some of the earlier writers. Medical management has proved so successful that surgical interference is limited almost entirely to the complications arising from a long-standing chronic peridiverticulitis and the acute type with perforation or abscess formation.

Medical Management.—The underlying principle is rest for the portion of the bowel affected. The mere presence of diverticula (diverticulosis) calls for no particular restriction of the patient's activity, although he should know of their existence and omit foods that leave a rough, coarse residue. Berries and fruits with skins are best avoided. The daily use of mineral oil in doses sufficient to prevent constipation is recommended. These measures will greatly decrease the likelihood of diverticulitis being superimposed.

The medical management of acute peridiverticulitis consists essentially of rest in bed, colon irrigations, a diet free from residue and application of heat or ice bags over the affected area. The irrigations may be given daily or bidaily with physiologic solution of sodium chloride at 110 F. Since the heat from the solution is perhaps the most important factor, a Y-tube arrangement through which the solution can return allows larger quantities of the solution to be used more expeditiously, as well as minimizing the discomfort and effort on the part of the patient.

The diet is always important, and for the acute exacerbations of diverticulitis it assumes a major role. The caloric value should be adequate, but the foods must be nonirritating and free from residue to be handled by the colon. Such foods follow: heavy cream, butter, broth, steamed rice, plain gelatin, eggs boiled or poached and sugar stick candy. Liquids except milk may be allowed, but these should be warm.

Antispasmodic drugs are given, although some authorities doubt their efficacy. Tincture of belladonna in doses up to 15 minims three times daily is the one most commonly used.

After a week or more of this regimen the acute symptoms will subside when the condition is uncomplicated. The mass in the left lower quadrant, if palpable, will be reduced in size; the tenderness will have largely disappeared; the temperature and white blood cell count will have returned to normal, and the abdominal discomfort incident to the obstruction and spasm of the colon will be minimal. During this period no regard need be given to bowel movement, since the residue-free diet and daily irrigations adequately take care of this.

The patient may then become ambulatory. Mineral oil is given, preferably two or three times daily, in doses sufficient to keep the daily stools soft but formed. Large doses given once daily have a tendency to cause the oil to leak through the rectum. The antispasmodic drugs are discontinued, and as soon as normal bowel function is established the irrigations are omitted.

Additions to the diet may be made rather rapidly after the acute symptoms subside. Vegetables may be puréed for a time, but whole, cooked, low residue vegetables are usually tolerated early. Fruit juices, cooked fruits without skins, custards, meat, white bread and potatoes are allowed —in all a rather liberal diet, but one free from coarse, rough fibrous food, such as celery, cabbage and lettuce, unless finely chopped. Uncooked vegetables, fresh fruits with skins, coarse bread, spices, berries with seeds, condiments and iced drinks should be continuously omitted, and any food which causes gas or discomfort should immediately be deleted from the diet list.

We feel that there is no necessity for a laxative at any time, preferring, if the need should arise, to use an enema of plain water or preferably of physiologic solution of sodium chloride.

If the patient is sufficiently impressed by the potential seriousness of his condition and the importance of constant care concerning his diet and bowel habits, his chances of avoiding subsequent serious attacks will be greatly enhanced.

Surgical Management.—While diverticulum formation in the colon was described nearly a century ago, only within recent years has sufficient information concerning the clinical course of its complications been accumulated to permit accurate conclusions concerning their surgical management. The treatment of uncomplicated diverticulitis by general agreement continues to be left in the hands of the internist. Since 1907, however, when W. J. Mayo reported the resection of a portion of the sigmoid for diverticulitis in 5 cases, the surgeon has considered that the presence of complications such as stenosing peridiverticulitis, colovesical fistula and abscess transfers the lesion to his field. It is an interesting commentary, incidentally, that hemorrhage from the bowel, which has been a frequent presenting symptom of diverticulitis in our experience, is not a complication requiring surgical intervention. Bleeding, whether constant and sight or spontaneous, massive and dark, presents a serious diagnostic problem but has not required radical treatment.

When the general opinion was prevalent that cancer was likely to be found in association with diverticula, many surgeons concluded that, since so intimate an association existed between the inflammatory process and malignant lesions, the primary resection of stenosing tumefactions in the sigmoid was justifiable—a conclusion which tremendously increased surgical mortality. We now believe, as has been stated earlier, that this relation is so rare that it may be regarded as purely coincidental. As the specter of malignant degeneration receded, reports accumulated indicating that primary procedures on inflamed bowel carry a high mortality. For this reason, colostomy accompanied with a minimum of exploratory manipulation came into favor as a preliminary to resection. This procedure was advocated where resistant obstruction developed, where fistulas to the bladder or abdominal wall occurred and where pelvic abscess was present or impending. In the beginning the fecal diversion was accomplished by exposing a loop of the left side of the colon above the lesion. Experience tended to demonstrate, however, that manipulations of the nearby colon was not without risk and that if further surgical procedures were indicated involvement of the descending and sigmoid colon in a colostomy emphatically limited the scope of secondary resection. For these reasons the transverse colon is now regarded as the safest and most logical site for the abdominal anus.

It was then noted that when a colostomy is performed and the fecal current diverted the peridiverticulitis and the accompanying perisigmoidal inflammatory reaction will subside; in many instances to the extent that the bowel will appear almost normal when visualized roentgenologically. This does not happen quickly, however, and if the process warrants colostomy, many surgeons agree that the diversion of the fecal current should be maintained for approximately a year and that at the end of this time the stoma should be closed. Since complete and long continued diversion of the current was regarded as important, the technic for transverse colostomy which had been described by Sir Hugh Devine appeared exceptionally appropriate.

Among the advantages claimed were that the left side of the colon is completely defunctionalized, as no fecal material can enter the distal stoma, and that liquid feces are not constantly discharged onto the skin with inconvenience to the patient from the resultant digestion and often severe and extensive irritation of the skin surrounding the colostomy opening. Devine emphasized his opinion that the lower portion of the bowel, by disuse and daily irrigations with saline or antiseptic solutions, could be rendered practically free from organisms within a few weeks.

The procedure originally described by Devine consists of making an upper right rectus incision, suturing together the adjacent surfaces of a loop of the transverse colon to form a long (about 10 centimeters) spur, passing Ochsner clamps through stab wounds, one on each side of the longitudinal incision, and, with the clamps applied above the spur, cutting the bowel in two with the cautery and pulling the severed ends through the stabwounds. The longitudinal incision is then closed, with the upper end of the spur, from which the two limbs of the colostomy diverge, pulled up against the under-surface of the peritoneum.

The outstanding disadvantage of this procedure is the danger of contamination and possible wound infection from pulling the severed ends of the colon through the stab wounds. It is possible also to injure the blood supply to the cut ends of the bowel in pulling them through the small stab wounds. To obviate this, the technic has been modified—and we think improved—by Alton Ochsner and his associates: A transverse incision is made down to the fascia, which with the peritoneum is incised longitudinally. The spur is formed in the same manner as before; clamps are applied above the spur; the bowel is divided completely with the cautery, and the limbs of the severed colon are brought out at the respective ends of the transverse incision. Closure is made with the spur in the same relation to the under-surface of the peritoneum. However, with the Devine procedure, the final closure of the two openings is difficult and not without peril, and the transverse colon is left with considerable deformity. If forming of an artificial anus is the sole surgical step contemplated and it is to be left a year, these disadvantages may be more than compensated.

Within recent years we have observed that persons with diverticulitis who have carried a colostomy for a long period and, having clinically recovered, have had the stoma of the abdominal anus closed have not infrequently presented themselves later with disturbing recurrences. The inflammatory reaction may reappear with consequent stenosis; a tumefaction in the sigmoid may descend into the lower part of the pelvis and produce pain; apparently quiescent bladder symptoms may recur, or the patient may suffer from chronic obstipation. From this experience we have concluded that in practically all instances when a lesion has progressed to the stage where surgical measures are indicated, preliminary colostomy should be followed after a few months by resection of the segment of bowel involved. This new concept has been discussed with a number of competent observers, among whose reactions are the following. J. Arnold Bargen stated:

> About 15 per cent of the patients with recurrent attacks of diverticulitis develop obstructive or perforative symptoms severe enough to warrant surgical measures. Some years ago colostomy alone was performed, and the segment of the bowel distal to the colostomy was left intact. Later on, the colostomy was closed without further surgery. In a few of these cases there was a recurrence of the diverticulitis. The difficulties in making a second colostomy were such as to make us feel that once the patient has come to the stage of colostomy, it is probably best to resect the diseased segment of the sigmoid.

John deJ. Pemberton expressed a similar opinion:

> When obstructive symptoms, abscess or fistula develops, I feel that surgery is indicated. It is not feasible to make a direct attack on the involved segment because of technical difficulties; instead, a colostomy should be established. Occasionally, because of the marked subsidence of the inflammation, one is tempted to close the colostomy without resecting the segment of bowel involved. We have done this on several occasions, often followed by recurrence of the inflammatory process. When the process has been severe enough to necessitate the establishment of a colostomy, it is far wiser to follow up later by an operation for removal of the affected segment of bowel than to close the colostomy.

It is still our opinion that the Devine colostomy is a serviceable procedure when the artificial anus is to be carried by the patient for a long period or is to be permanent. Since our new concept concerning diverticulitis, however, anticipates that the colostomy should be used for a comparatively brief period, after which the lesion should be resected, we now feel that the Mikulicz procedure on the transverse colon is preferable. While this simpler procedure results in an intestinal stoma more difficult to regulate and while more attention must be paid to the nearby epidermis, if the patient is not required to suffer this annoyance for an extended period, its use is justified by the much less complicated technic of closure.

The foregoing remarks concerning treatment, both medical and surgical, have dealt with the so-called chronic phase of the disease, typified by tumefaction and repeated exacerbations of symptoms largely dependent on the degree of obstruction and the amount of pericolic inflammatory reaction. Another phase of diverticulitis, the sudden perforation of a diverticulum or perforation with subsequent abscess formation, although the number of cases are in the minority, establishes itself in the category of acute abdominal conditions that demand prompt surgical intervention. Spontaneous rupture into the free peritoneal cavity is extremely rare. The inflamed diverticula cause the sigmoid flexure to adhere to the lateral or anterior abdominal wall or to the wall of a viscus, frequently the urinary bladder, and should rupture occur, the likelihood is great that a left lower quadrant abscess will form. After such a process, and perhaps with the degree of obstruction of the bowel playing some part, fistulas frequently appear.

Opinions vary as to the proper method of dealing with these acute perforations with or without abscess. Obviously procedures involving much manipulation are to be avoided in the presence of the infection, and resection of a segment of the bowel in the face of the existing local peritonitis or abscess formation is out of the question. After an acute perforation, the question of whether to attempt to close the perforation and drain the abdominal cavity or to wait in the hope that an abscess will form and allow later surgical drainage with less danger can be argued *pro* and *con* just as it is when applied to appendiceal perforation. However, when a decision is reached that the abdomen should be opened, the simplest drainage procedure with the minimum amount of manipulation should be done, and any attempt to correct the cause of the process should be deferred until the acute inflammatory reaction has completely subsided.

PROGNOSIS

Statistics on the frequency with which diverticulosis is followed by diverticulitis are not available. If, however, one knows that a diverticulosis exists, with a rational dietary regimen and some effort to maintain normal bowel function, the incidence of superimposed diverticulitis is thought not to be high.

The prognosis of uncomplicated diverticulitis is good. With adequate medical management Brown and Marcley obtained successful results for approximately two-thirds of their patients, and many of the remaining third were able to live in comparative comfort.

For the surgical aspect of the condition the prognosis is somewhat less favorable. However, surgical procedures are undertaken primarily for perforation and abscess and fistula formation, all rather serious complications in that the operations necessary for correction are formidable. The risk is largely attendant on the immediate treatment, after which the prognosis is favorable.

Radical surgical procedures without preliminary colostomy for chronic lesions and injudicious exploration and manipulation for acute perforation and abscess formation result in an extremely high mortality rate, but when good judgment and skill are exercised, the mortality will approximate 10 to 15 per cent.

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CHAPTER XXXIII

CANCER OF THE COLON

Carcinoma is the most frequently recognized tumor of the colon, and statistics show that its incidence apparently is on the increase. Between 1920 and 1929 in this country death from cancer of the intestine, excluding the rectum, increased from 7.1 to 9.1 per cent per 100,000; in England and Wales during this same period there was an increase of 100 per cent. Two factors suggest that this was an actual as well as a relative increase: (1) During the twentieth century life expectancy has been increased from forty-two to fifty-eight years, thereby greatly increasing the number of persons of the so-called cancer age. (2) There have been vast strides in diagnostic facilities.

Different parts of the colon vary in susceptibility. In a series of 625 cases of cancer of the colon reported by Judd, the location was as follows: sigmoid flexure, in 292; cecum and ascending colon, in 159; transverse colon, in 75; descending colon, in 46; hepatic flexure, in 29, and splenic flexure, in 24.

INCIDENCE

There is, in our experience, a predominance of colonic cancer in the male, although Nothnagel expressed the opinion that there is little difference in the frequency of occurrence in the sexes, and DeBovis and Clogg expressed accord with his view. Cumston and VanderVeer reported a series in which 63.8 per cent of the patients were males and 36.2 per cent females. In our series the male was affected in a proportion of approximately 2 to 1.

Cancer of the lower part of the gastrointestinal tract may occur at any age, but is usually found in the fifth and sixth decades. Clare reported finding a medullary carcinoma of the colon in a child of three years. Phifer reviewed 23 cases of cancer of the sigmoid flexure and rectum in children under sixteen, and Waynewright studied a group of 7 children under sixteen with malignant disease of the colon above the sigmoid flexure.

The cause of cancer of the colon, as of cancer elsewhere, is a matter of conjecture. The malignant transformation of adenomatous polyps, proposed first by Bardenheuer and later by Quenu and Lander, has been definitely established. Hauser and Kraske, Verse, Rankin and others have reported many cases of malignant disease superimposed on colonic polyps.

PATHOLOGY

The gross and microscopic pathologic anatomy of cancer of the colon varies with the type and location of the growth, ranging from the large, flat granular tumors occurring in the right side of the colon to the firm encircling napkin-ring growths of the left half. Although unusual, multiple primary carcinomas of the colon have frequently been observed. Miller reported 5 cases of multiple malignant growths of the colon, in one of which he expressed the opinion that there had been three primary lesions. Rankin, Bargen and Buie reported 16 cases of multiple primary cancer of the colon, and we have observed 2 cases during the past year.

Carcinoma of the colon, like carcinoma of other parts of the gastrointestinal tract, is usually adenomatous, although squamous cell epithelioma is occasionally found, its presence being explained on the theory that regenerative cells of the glandular epithelium in these organs have the power to produce either secretory (glandular) epithelium or protective (squamous) epithelium. Grossly, the carcinomas of the right half of the colon are large and as a rule flat, irregular growths with a stubbed, protruding surface, giving the appearance of granulation tissue, or they may be ulcerating, with a wide, flat necrotic base. Microscopic examination reveals a variation from the highly cellular tumors composed almost entirely of glandular tissue down to the growths which are composed mostly of fibrous tissue, sparsely intermingled with groups of gland cells. Ulceration is the predominant tendency of the former type, while cicatrization is characteristic of the latter. Colloid carcinomas may appear in the colon, generally arising in the cecum or the right half of the large bowel. They may become large and usually do not ulcerate so readily as the cellular adenocarcinomas. Grossly, they are soft, gelatinous, cauliflower-like tumors; microscopically, they are composed of a thinly cellular collagenous substance supported on a framework of fibrous connective tissue. The colloid or mucoid type comprises about 5 per cent of colonic carcinomas and is characteristically slow growing, more difficult to remove and prone to recur. The ultimate curability of this type of growth is very low.

Cancer of the left half of the colon may be papillary, polypoid, mucoid, ulcerating or infiltrating; may undergo degenerative changes, and usually is surrounded by considerable pericolonic infection. Microscopically, the cells of adenocarcinomas of this portion of the bowel may be differentiated to such a marked degree and arranged in glandular or acinous formation with such perfect cellular alinement that they appear almost like normal mucous glands. Or they may be so undifferentiated that practically all traces of gland formation are lost. The cell nuclei are usually large and irregularly rounded; they stain deeply, and the cells as a whole have lost their columnar form. When acini or gland formations are found in such carcinomas, the cells are not in good alinement and show little tendency to individual differentiation.

It was on this variation in degree of difference between neoplastic tissue and normal mucosa that Broders based his classification of malignant change. He showed that in tumors with no similarity to normal structure, no gland formation and no system of arrangement, but where malignant cells develop in a wild, irregular, random manner, with numerous mitotic figures and irregularly shaped, deeply stained nuclei, the tendency is to rapid growth, with early local invasion and distant metastasis.

SYMPTOMATOLOGY

To understand the evolution of the signs and symptoms of cancer of the colon, one must consider the large bowel not as a single organ but as two segments with different physiologic functions. The right half of the colon, the absorptive portion, when invaded by lesions produces a group of symptoms revolving around a physiologic disturbance of the colon. In the left half the phenomena are almost entirely those of obstruction in one of its three phases. Contributing factors modify the symptoms in each half, such as the type of lesion, anatomic differences in the wall of the bowel and the intestinal content, which on the right side is fluid and on the left is solid and formed. The paucity of early symptoms in the course of malignant disease of the colon is characteristic but of paramount importance, as the earliest warning of diagnostic significance is a change in bowel habit. This in itself is pathognomonic, and such a history should brand a person, until proved otherwise, as the unfortunate host of a colonic neoplasm.

Lesions of the Right Half.—On the basis of symptoms and signs, one may divide carcinoma of the right half of the large bowel into three groups: (1) the so-called dyspeptic group, often diagnosed as chronic appendicitis, chronic cholecystitis or "intestinal indigestion"; (2) the group with profound anemia without visible loss of blood, and (3) the group in which the growth is accidentally discovered.

The number of carcinomas of the right half of the colon that fall into the dyspeptic group is large (about 60 per cent), and often the condition is advanced before the underlying lesion is discovered. Usually there is no mass, and because of the very indefinite nature of the symptoms, roentgen examination is not sought and the diagnosis is often unsuspected until late. In the second group the outstanding manifestation is profound anemia not associated with visible blood loss and characterized by profound weakness and loss of weight and strength. This group also is relatively large (about 30 per cent). The blood picture may be confused with primary anemia until hematologic studies have been made. The exact explanation of this type of anemia is not clear, but it probably is due to a perverted function of the mucous membrane, which is impaired to such an extent that toxic substances from the broad infected surfaces of the cancer are readily absorbed, depressing hemopoiesis or destroying immature red cells.

In the third group a mass is accidentally discovered in the right iliac fossa and on further examination proves to be a carcinoma. This occurrence is more common than is generally believed, and this type affords the most favorable prognosis, because usually it is discovered in the earlier stages. Between 5 and 10 per cent of any large series of carcinomas will fall in this group and are found on examination of patients who present themselves for a general check-up or who are being examined for some reason entirely unrelated to the gastrointestinal tract.

Lesions of the Left Half.—In the left half of the colon obstruction is the predominant feature. This is the result of three factors: (1) the type of lesions, (2) the anatomic conformity of the bowel and (3) the type of bowel content. Malignant lesions of the left half of the colon differ materially from those of the right half. They tend to encircle the lumen of the bowel, while those of the right half are usually flat and ulcerating; they tend to be of the hard, scirrhous and cicatrizing type, whereas those on the right side almost invariably occupy the lateral wall of the colon, making an ideal site for absorption but lacking the necessary stenosis which produces obstruction.

The obstructive features result directly from encroachment on the lumen of the bowel. Irritability of the bowel is common. Occasional upsets are noted, diarrhea most often alternating with periods of constipation. Changes in bowel habits are the most common early symptom of carcinoma of the lower part of the gastrointestinal tract. Gradually, borborygmus and increasing flatulence develop, and as the lumen of the bowel slowly decreases, a picture of obstruction, acute, subacute or chronic, develops. Visualization of peristaltic waves is possible only if the subject is extremely thin or if the contraction of the lumen of the bowel produces such obstruction as to bring about proximal dilatation.

Tumefaction is more common in the left half of the colon than in the right, because of the greater accessibility of this portion and the predominance of obstructive features, which dam back the bowel content, producing impaction and dilatation. Not infrequently, elderly patients are able to point out definitely the site in the colon where peristalsis stops. This is an old sign, well recognized by senior surgeons, and is responsible for the aphorism that "increased inability of elderly patients to move the bowels without cathartics is highly suggestive of carcinoma." Almost invariably with acute obstruction of the colon the lesion is situated beyond the middle of the transverse colon.

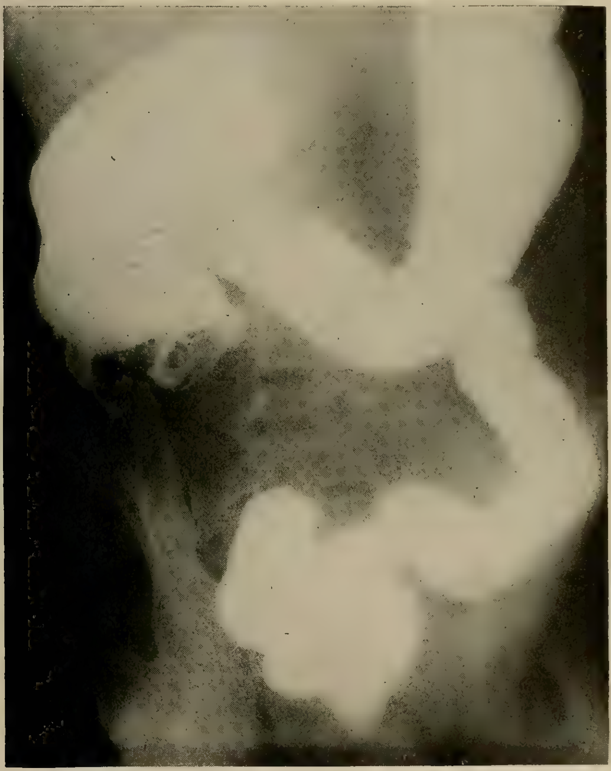

FIG. 155.—Large cancer of the cecum, involving the entire lumen just distal to the ileocecal valve.

Blood may be present in or on the stool, but not until the mucous membrane of the bowel is ulcerated; in many cases it is not an early symptom. Bright red blood in or on the stool is pathognomonic of lesions of the rectum or lower left part of the colon. Occult blood is more significant in the diagnosis of unusual tumors of the small bowel. Carcinoma of the colon frequently produces sudden complete obstruction without forewarning.

Although this may be due to a volvulus or other lesion, it is usually due to obstruction of the lumen of the bowel by plugging of a contracting carcinoma or by intussusception or swelling of an inflammatory process superimposed on a malignant lesion. The usual type of obstruction, which

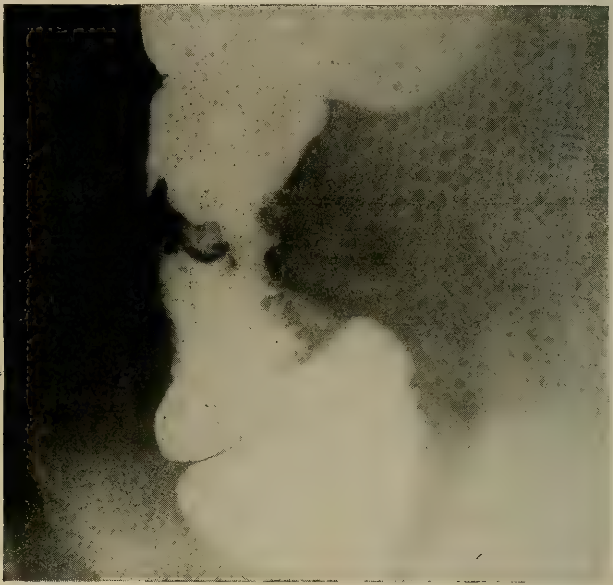

FIG. 156.—Extensive carcinoma of the ascending colon.

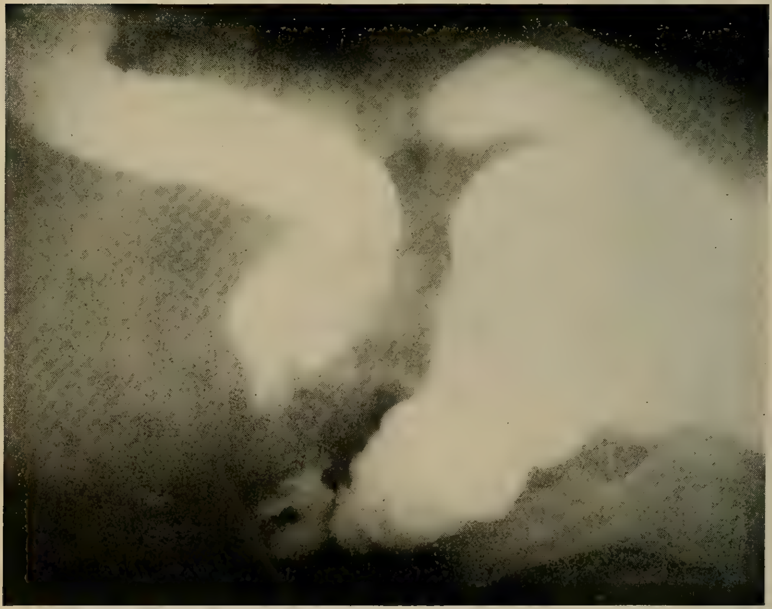

FIG. 157.—Filling defect produced by carcinoma of the hepatic flexure of the right half of the colon on the transverse side.

occurs in about two-thirds of the cases of carcinoma of the left half of the colon, is chronic, or at most only subacute. Obstructive phenomena, associated with tumefaction, borborygmus and blood in the stools, are always suggestive of malignant disease of this part of the colon, and the diagnosis is easily confirmed by roentgen examination.

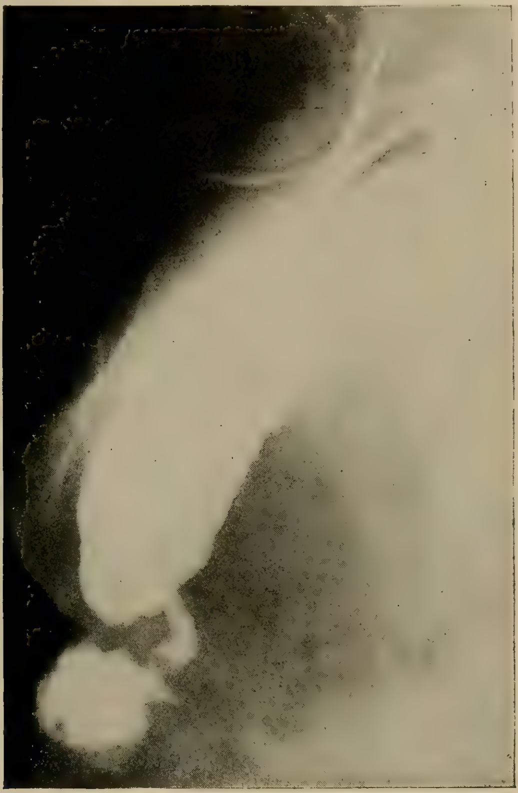

FIG. 158.—A typical annular carcinoma, producing obstruction of the descending colon.

DIAGNOSIS

One finds: (1) vague dyspeptic symptoms with weight loss and weakness; (2) a profound anemia without visible blood loss; (3) a palpable mass in the right lower quadrant; (4) changes in bowel habits, with alternating periods of diarrhea and constipation, and (5) acute, subacute or chronic obstruction.

In the presence of any group of these symptoms a thorough examination of the colon at the hands of a competent roentgenologist is indicated. One cannot too strongly condemn the usual textbook picture of weight loss, cachexia and dehydration as pathognomonic of cancer of the large bowel, for in effect these evidences are signs of advanced malignant change with possible metastasis and are the signposts of impending dissolution.

To the suggestive clinical history, confirmatory evidence furnished by roentgen examination is indispensable. The diagnostic accuracy for disease of the colon in roentgen departments of good clinics throughout the country ranges well over 95 per cent. Here must be mentioned, but only to be condemned with vigor, the dangerous practice of giving barium by mouth for the diagnosis of lesions of the colon or when one so much as suspects the possibility of cancer of the colon. Such an approach will without doubt in many instances render complete a partial obstruction. This deplorable ignorance or carelessness results in a catastrophe which is all too frequently seen even now. The diagnosis of cancer of the colon is often far from a simple problem, but when roentgen examination finally reveals the presence of a lesion, the field is then limited to about six other possibilities: hyperplastic tuberculosis of the colon, diverticulitis, polyposis, syphilis, segmental ulcerative colitis and actinomycosis. A detailed history and thorough study supplemented by the seasoned judgment of a competent roentgenologist should serve to clarify the diagnosis.

PREOPERATIVE PREPARATION

A careful study in every case is invaluable for discovery of coëxisting disease and evaluation of the patient's reserve. Routine blood counts, urinalysis and chemical analysis of the blood are obvious necessities. An *x*-ray study of the chest will reveal pulmonary metastasis or other abnormality, as well as an enlarged heart or a dilated aorta. Further studies are made when indicated.

Rehabilitation is carried out by the usual means of combating malnutrition, dehydration and anemia. A high caloric nonresidue diet rich in carbohydrates and supplemented by abundant fruit juices and stick candy is recommended. Fluids up to 3,500 to 4,000 cubic centimeters are given daily, and transfusions are used to combat anemia, if present. When possible, patients are encouraged to be up and moving about to maintain strength and vigor. A high vitamin intake is regarded as vital, and efforts to replenish the glycogen reserve in the liver are useful. Usually, adequate preoperative rehabilitation may be effected in from five to seven days, during which the colon itself is being prepared for operation. Administration of 1 ounce of castor oil is usually the preliminary step in this consideration, and after evacuation has been complete the bowel is irrigated repeatedly with generous quantities of physiologic solution of sodium chloride morning and night until the fluid returns clear. These irrigations are discontinued the day before operation, and paregoric is given during the late afternoon and evening to allay peristalsis.

OPERABILITY

Along with prognosis, one must take into consideration another factor, namely, operability. A fair standard is one based on the following criteria: (1) the presence or absence of distant metastasis, (2) the presence or absence of extensive regional lymphatic involvement, (3) extension to adjacent parietal or visceral structures and (4) the surgical tolerance of the patient. Obviously, metastatic pulmonary lesions revealed by routine *x*-ray examination of the chest or liver involvement found at abdominal exploration will exclude the possibility of cure by radical surgical measures. Likewise, extensive involvement of the regional lymphatic vessels make cure less likely, but actual microscopic examination of the gland in question by frozen section is necessary to establish the presence of such involvement, because of the frequency with which local lymphadenopathy proves to be only an inflammatory response to the degenerating lesion. Local extension with fixation of the growth adds greatly to the peril of operation. This may be a result of the actual malignant invasion, but usually is an inflammatory reaction. The resection of involved portions of the bladder, small intestine and parietes has often been done with immediate success, and it may be the dictate of good judgment to operate in selected cases of this sort. The general condition of the patient is obviously of paramount importance, for it requires a considerable degree of stamina to withstand a surgical procedure of such magnitude. Therefore, the debility incident to the presence of a malignant growth with or without coëxistent disease must be given vigorous preoperative attention. It may be observed, however, that anemia (with a hemoglobin concentration of 25 to 30 per cent) with cancer of the right half of the colon is not the contraindication to operation after proper rehabilitation that it is with cancer of the left side of the colon or the stomach.

Operability figures vary widely in the hands of different surgeons, and yet their influence is unmistakable. For example, the operative mortality of one man may be much lower than that of his colleague, but a further comparison will show likewise that his operability figures are smaller in proportion. In other words, while he will lose fewer patients of a given number in an attempt to extirpate the growth, in consequence he will have a smaller number of patients alive out of the given total at the end of any definite term of years. We have found that with an operability figure of about 70 per cent the surgical mortality should range below 10 per cent. Lower operability curves will refuse some patients operation who would be cured, albeit the extirpation of cancer in this group entails a high casualty list.

TREATMENT

Radical surgical extirpation is without question the procedure of choice from the standpoint of curability, and when the lesion has progressed to such an extent that this is not possible some palliative procedure for shunting the fecal current often is useful. One's surgical repertoire for cancer of the colon must permit of sufficient variation to cope with many and varied circumstances. Each patient is an individual problem to be handled as such; the operative procedure must be suited to the patient, and not the patient to the operation. Different procedures are applicable to lesions in different parts of the colon, and they may be performed in single or multiple stages, depending on the general condition of the patient and the local situation found at exploration. In the poor risk patients—those who are advanced in years or ravaged by coincident disease and those in whom rehabilitation does not seem to be compatible with single stage operations—the advantages of two or more less formidable stages are unquestionable.

For malignant disease of the right half of the colon we feel that an ileocolostomy and resection of the right side of the colon is the procedure of choice. This maneuver may be accomplished in one or two stages. An end-to-side anastomosis of the terminal part of the ileum and transverse colon has proved most satisfactory (1) because of the ease and safety with which it is performed, (2) because it more nearly approaches the true anatomic structure of the ileocecal junction, (3) because it by-passes the fecal current without impending evacuation of the right side of the colon when a two stage procedure is to be performed and (4) because if the question of one or two stage operation rests in a delicate balance, the decision may be made at operation after an ileocolostomy has been performed.

Cancer of the left half of the colon calls for a different mode of attack. Often the initial symptoms are those of complete intestinal obstruction. Under these circumstances immediate surgical relief is indicated. If, on the other hand, obstruction is only partial, as is usual, and decompression may be effected by medical measures, then after an adequate period of preoperative preparation, the growth is best removed by an obstructive resection with complementary cecostomy.

The procedures available for resection in the average case in which a mobile segment of the bowel other than the right half of the colon or hepatic flexure is to be removed are: (1) obstructive resection and complementary cecostomy (Rankin), (2) primary anastomosis with or after cecostomy and (3) exteriorization.

With cancer of the right side of the colon, obstruction is a rare complication, while on the left it is frequently observed. On either side, infection with the development of abscesses, perforation, local peritonitis or sinus formation may occur. To relieve existing or avoid impending obstruction, decompression by cecostomy is advisable. When infection plays the leading role, little other than palliative drainage is possible, although occasionally diversion of the fecal current will help to improve the situation. When complete obstruction of the large bowel due to malignant change is present or satisfactory decompression cannot be effected with enemas, cecostomy becomes essential.

Cecostomy is a useful colonic operation and is indicated:

(1) *For decompression:*
  (*a*) in the presence of acute obstruction secondary to cancer of the left side of the colon or rectosigmoid;
  (*b*) in the presence of subacute or chronic obstruction secondary to cancer of the colon anywhere, unrelieved by medical measures;
  (*c*) as a preliminary stage of a graded radical maneuver for cancer of the rectum or rectosigmoid producing obstruction not amenable to medical decompression.

Cecostomy under these circumstances differs somewhat from that employed as a complementary measure. It is desirable to bring the entire cecum out through a split muscle incision in the right groin when obstruction calls for it. This is easily accomplished if the cecum is mobile, and if there is no mesentery adequate mobility may be obtained by dividing the peritoneal reflection of the bowel onto the parietal peritoneum. The whole cecum is brought out and a glass tube placed under it, the entire fecal current thus being by-passed. The subsequent closure may be done under local anesthesia and is a procedure of small magnitude. Flushing through the cecostomy and drainage of the bowel adequately relieve the pericolonic infection around the obstructing growth in the majority of instances.

Delivery of an acutely obstructed and hugely dilated cecum is often difficult, or it may be impossible—because of the size, distention and resulting thinness of the bowel wall—to bring it out at all without decompression. Most of this distention is from gas; the cecum is only half filled with liquid feces, and under such circumstances it is useful to aspirate this gas with a thin needle. As soon as the pressure is relieved, the bowel mucous membrane becomes engorged with blood; the whole wall thickens, and the loop of intestine is more easily handled. One can either put a tube into it *in situ*, bring out the cecum or, as Stone suggested, suture the peritoneal coat of the cecum to the parietal peritoneum and open it widely at a subsequent date.

(2) *As a complementary measure:*
   (*a*) either after resection and anastomosis of the intestine, end to end or laterally;
   (*b*) or occasionally after exteriorization of the colon without resection.

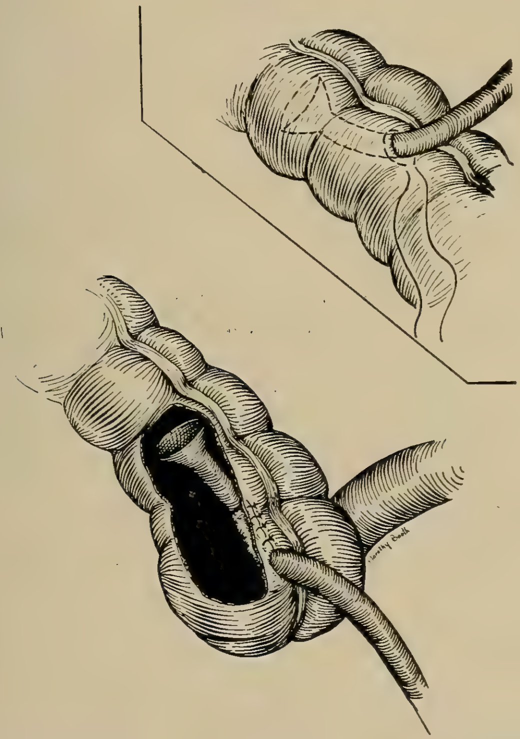

Fig. 159.—Cecostomy by means of the open-end Pezzar catheter; Witzel's technic.

Under these circumstances a different type of cecostomy is usually employed. The abdomen has been opened for exploration through a low midline or a paramedian incision, right or left, and the cecum is pulled into the incision and opened with a cautery. A wing-tip catheter is inserted after Witzel's technic, and the catheter is withdrawn into a stab wound in the right groin. The tube is opened at the end of twelve hours and decompresses the colon of any gas and fluids which have accumulated. It takes the strain off the suture line if anastomosis has been resorted to, and if obstructive resection or exteriorization has been employed it prevents accumulation of dejecta with consequent distention. The tube is removed after it has accomplished its purpose, being either pulled out through the wound or cut off and allowed to pass *via* the natural route. In either event, spontaneous closure customarily follows.

Measures of Extirpation of the Right Half of the Colon.—For malignant growths of the right half of the colon, resection may be performed in one or two stages, depending on the condition of the patient and the findings at exploration. In either case the technical procedures are practically the same: (1) ileocolostomy, by which the fecal current is shunted past the growth, and (2) mobilization and resection of the right side of the colon to within a short distance of the ileocolostomy, followed by closure of the proximal end. In performing the anastomosis, any one of several procedures may be used. An end-to-side anastomosis, however, has been found by us to be the procedure of choice. The open anastomosis obviously carries a greater possibility of contamination. Closed anastomosis by means of the Parker-Kerr basting stitch is useful. The instruments of Stone and Furniss make aseptic anastomosis simple and satisfactory. They are recommended as distinctly useful adjuncts to the surgeon's armamentarium. In our hands anastomosis by means of the Rankin clamp has been found entirely satisfactory.

Ileocolostomy Performed With the Rankin Clamp.—The terminal portion of the ileum about 10 to 15 centimeters from the ileocecal valve is divided between clamps, one of which is a special three-bladed instrument. The distal end of the ileum is then closed with inverting sutures and allowed to drop back into the peritoneal cavity, to be removed when the right half of the colon is resected. At a point about midway of the transverse colon, the anterior surface of the large bowel is then grasped with the second blade of the Rankin clamp, and by means of the cautery an elliptic piece of the colon is removed. Sutures are then applied anteriorly and posteriorly (Fig. 160). The clamp is opened and removed as the sutures are drawn taut, the two edges of the bowel thus being inverted so that on both surfaces the peritoneal coverings are approximated. An additional layer of sutures is then introduced to reinforce each of the suture lines and completely peritonealize the anastomosis. Silk is frequently desirable for this second row of interrupted sutures because of the delayed healing power of patients with right colonic cancer.

Mobilization and Resection of the Right Side of the Colon.—This constitutes the second half of the operation and may be performed with the first procedure or after two to three weeks. The peritoneal attachments to the lateral abdominal wall are divided, and the whole right half of the colon is rotated mesially as the dissection is carried from the cecum to the hepatic flexure. Care must be taken to avoid injury of the spermatic vessels, which appear at the lower angle of the wound, and as the dissection is carried upward the ureter, kidney and retroperitoneal part of the duodenum are to be assiduously watched for, since injuries are corrected with difficulty and carry a high mortality. The mesenteric vessels are clamped and divided as they appear, and after the hepatic flexure and proximal portion of the transverse colon are mobilized, a suitable point for the resection of the bowel is found. This is accomplished by means of clamp and cautery. The right half of the bowel is removed and the distal end of the transverse colon is closed by means of an inverting suture. To avoid possible dangers subsequent to over-distention, when the procedure is performed in one stage, an ileostomy 8 to 10 inches proximal to the anastomosis is then performed by means of a no. 20 rubber wing catheter. The tube is by preference brought out through a stab wound in the right lower quadrant, for when included in the abdominal incision the risk of postoperative wound infection is increased. In the two stage procedure this precaution is unnecessary, for when the anastomosis alone is performed the postoperative course is not jeopardized by intestinal atony incident to the manipulation and decreased intra-abdominal pressure following extirpation of the right half of the colon.

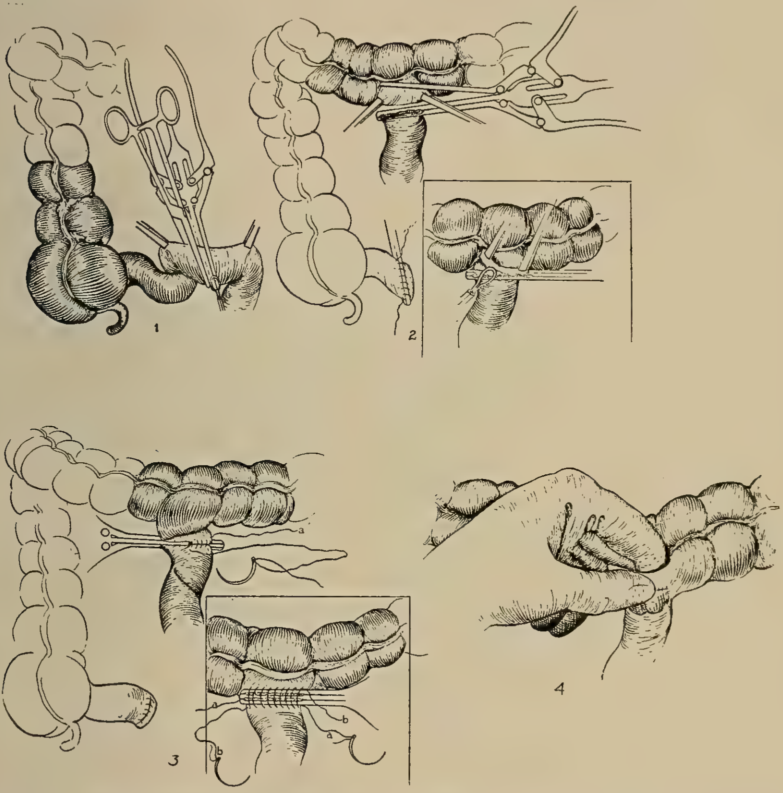

Fig. 160.—Aseptic ileocolostomy performed by means of the Rankin clamp: *1*, the terminal portion of the ileum is grasped in one arm of the clamp; a second clamp is applied just distal to this, and the intestine divided with a cautery. *2*, a suitable portion of the transverse colon is then grasped in the other arm of the three-bladed clamp, and by means of the actual cautery an arc-shaped portion of the bowel wall is removed. *3*, a continuous suture (*a*) is then applied to the posterior peritoneal surfaces; the clamp is turned back to its original position, and a second tier of sutures is introduced over the clamp to join the peritoneal surfaces of the colon and terminal end of the ileum anteriorly. As the clamp is then opened and removed, the sutures are drawn tight, inverting the closed ends of the bowel. The anastomosis is then strengthened by interrupted sutures and the raw surfaces are peritonealized. *4*, the anastomosis is opened by invaginating the adjacent wall of the colon through it.

Resection of the Transverse Colon.—Resection of either half of the transverse colon is based on the principles discussed under procedures suitable for either half of the large bowel; that is, growths of the right half of the transverse colon and hepatic flexure are best cared for after the manner described for malignant disease of the right half of the colon, and there is a like correspondence between lesions of the left half of the colon and lesions of the left half of the transverse colon and splenic flexure, for which obstructive resection is the operative maneuver of choice. However, it must be pointed out that the lymphatic network of the omentum bears the menace of subsequent recurrence and must therefore be completely removed. When obstructive resection is impossible and the criteria for exteriorization are fulfilled, one may have to resort to the latter procedure. Again, when the growth is small and situated in the right half of the transverse colon, where there is no evidence of adjacent lymphatic involvement, and when this portion of the bowel may be resected with adequate removal of the mesentery, primary anastomosis with a complementary ileostomy is at times justifiable.

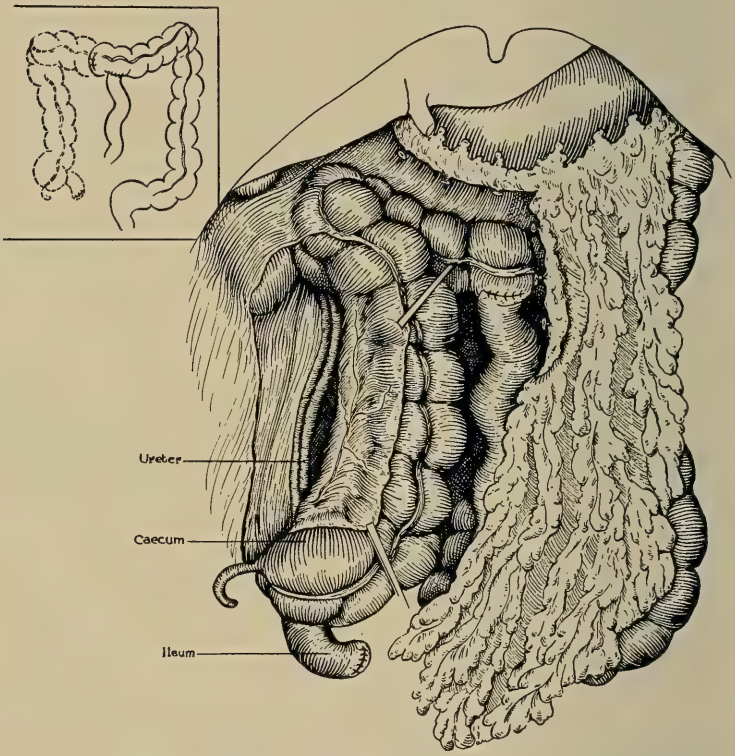

Fig. 161.—Mobilization of the right half of the colon with partial resection of the omentum following ileocolostomy. The procedure is completed by resection at another stage. The insert shows the proposed extent of resection.

Resection of the Left Half of the Colon.—In resection for malignant disease of the left side of the colon, primary anastomosis is dangerous because of the nature of the cecal content, the paucity of the blood supply and the tendency to poor healing because of lowered resistance to infection. In addition, the procedure limits the removal of adjacent gland-bearing tissues more than do some other graded procedures. If, however, the procedure seems advisable, it can be accomplished (1) by open anastomosis, (2) with the Rankin, Stone or Furniss clamp or (3) by a closed procedure, that of Parker and Kerr or a similar one. A complementary cecostomy should always be performed proximal to the anastomosis to obviate the dangers incident to increased intracolonic pressure. In place of primary anastomosis, exteriorization or obstructive resection may be used. The method of choice in our hands has been obstructive resection and complementary cecostomy, which has all the virtues of exteriorization, yet avoids its disadvantages and is applicable in any portion of the colon that is mobile or may be mobilized, except the right half.

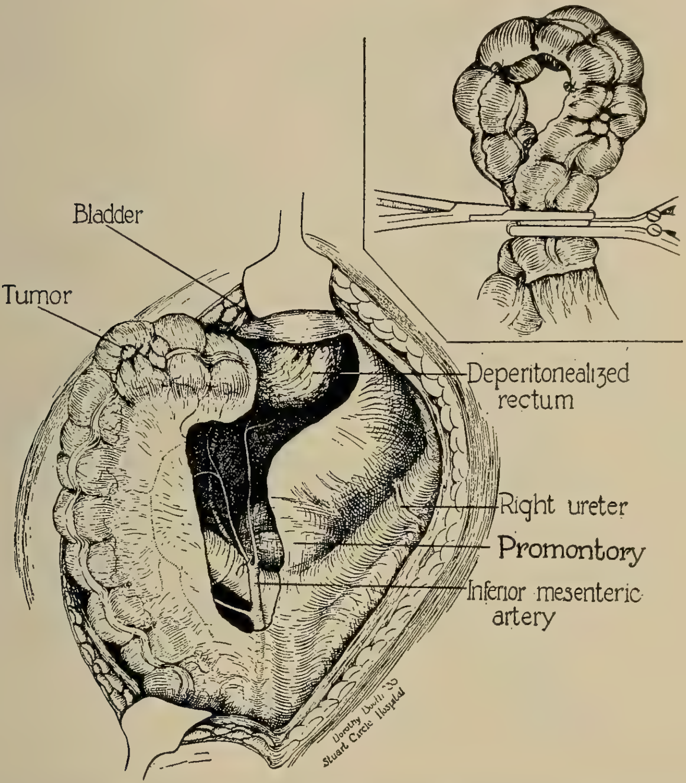

Fig. 162.—Mobilization of the sigmoid flexure and descending colon, with ligation of the bloodvessels in order to exteriorize the colon sufficiently to apply the Rankin clamp. The insert shows the distal and proximal portions of the bowel grasped between separate blades of the clamp. The cancer-bearing portion is then removed with the actual cautery.

Obstructive Resection.—**Advantages.**—A wide extirpation of the growth and adjacent structures is possible; with the clamp and cautery the possibility of infection is minimal; the physiologic disturbances incident to obstruction are anticipated and prevented by means of the complementary cecostomy; the procedure is not difficult and when quickly and expediently performed carries a low immediate mortality, while the percentage of ultimate cure in a large series rises high.

Technic.—The cancer-bearing portion of the bowel is delivered into the wound, and the peritoneal attachments to the lateral abdominal wall are divided in order to give sufficient mobilization. The vessels are then ligated close to the root of the mesentery and the intervening expanse of mesentery with its regional lymph nodes is widely excised. By means of the three-bladed clamp, the two limbs of the well mobilized bowel are grasped, one in each arm of the clamp. Clamps are then placed distal to the affected point, and the growth and adjacent part of the bowel are removed with the actual cautery. The rent in the mesentery is closed, and all raw surfaces are peritonealized. The clamp is then brought out of the wound.

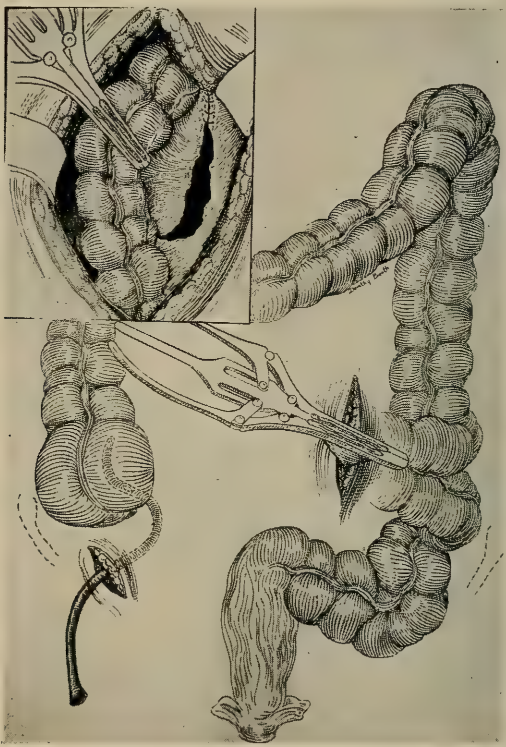

Fig. 163.—Completion of obstructive resection. The cecostomy is shown, the tube in the cecum being brought out through a stab wound in the right groin. The completed operation with the wound closed around the clamp holding the two ends of the bowel is shown. The insert shows peritonealization of the raw surfaces left from mobilization.

Complementary cecostomy with a wing-tip catheter is then performed, the tube being brought out through a stab wound in the right groin. The peritoneum is closed snugly about the protruding limbs of the colon, care being taken not to introduce sutures into the bowel wall. The abdomen is closed in layers about the clamp, which usually drops off between the fifth and ninth day. The cecostomy tube may be withdrawn or cut off, and after wound healing is accomplished the spur between the double-barreled colostomy may be divided with an enterotome or with clamps. If the colostomy opening does not close spontaneously it may be closed surgically under local anesthesia a month or more after the initial operation.

Exteriorization.—This procedure may be used on any portion of the transverse or descending colon or the splenic flexure which is or may be sufficiently mobilized to bring the growth well out onto the abdominal wall. It presupposes only a local excision of the growth, without adequate removal of lymphatic structures exposed to malignant invasion. In a large series of cases it has been found to carry a higher operative mortality than is justified, and the incidence of recurrence in the abdominal wall has been recorded as 12 per cent. There has also been a large percentage of intra-abdominal recurrence in the local lymphatic vessels which were not removed at operation. Sistrunk listed four contraindications: (1) when an adherent growth is associated with infection in the wall of the bowel, (2) when a large growth is associated with infection, (3) when obstruction is present and (4) when the growth-bearing portion of the colon has a short mesentery that cannot be adequately mobilized in an obese patient with a thick abdominal wall. To superimpose surgical trauma on existing infection predisposes to local suppuration or peritonitis. Undue tension jeopardizes the blood supply to the exteriorized loop of gut. When, however, exteriorization is to be performed, the procedure is as follows: The growth-bearing portion of bowel is delivered onto the abdominal wall as in the obstructive resection, but the bloodvessels and lymphatic structures are left intact; the abdomen is closed snugly around the extruded mass, which is carefully surrounded by petrolatum gauze in an attempt to prevent transplantation of malignant cells to the abdominal wall. The second stage may be performed at any time after seventy-two hours and consists of the removal of the protruding bowel by dividing it flush with the abdomen. The remaining double-barreled colostomy opening is then cared for after the manner described for obstructive resection.

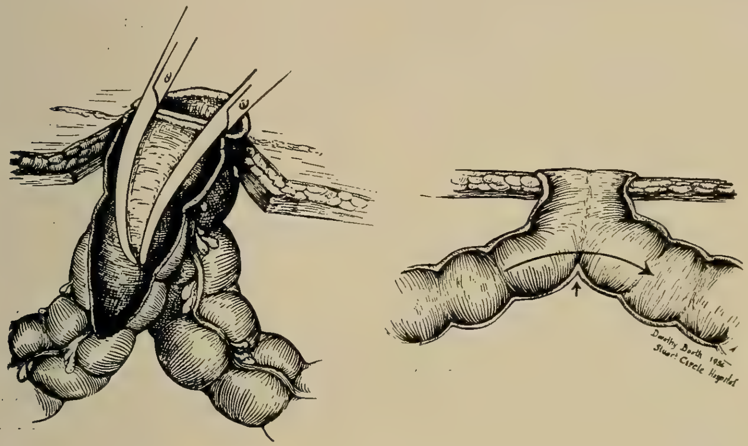

Fig. 164.—Three to four weeks after an obstructive resection the spur of the double-barreled colostomy is grasped between clamps. The clamps are tightened daily, and some time within five to seven days they may be lifted out as the septum is destroyed by necrosis. The reëstablishment of the lumen of the lower part of the gastrointestinal tract is shown at the right.

Exteriorization is definitely useful for elderly patients harboring a cancer in a mobile segment of the colon. It can be performed frequently under local anesthesia, the loop lifted out and the abdominal wall closed around it without ligation of the bloodvessels and the resection accomplished later. What unfavorable results have followed its use have been due rather to extension of the principle and faulty selection of cases than to the operation itself, for the maneuver has definitely lowered the mortality of colonic surgical measures.

Postoperative Treatment.—Careful postoperative supervision is more necessary for colonic than for routine abdominal operations. It is important to withhold fluids by mouth for from forty-eight to sixty hours, in order to minimize peristaltic activity. Up to 4,000 cubic centimeters of dextrose and saline solution daily is administered parenterally during this period, and it has been found a good rule to begin giving fluids by mouth only after the passage of gas by bowel. During this period careful oral hygiene must be insisted on, because of the high incidence of parotitis following operations on the colon.

A transfusion of 500 cubic centimeters of whole blood strikingly augments the immediate postoperative response. Frequent changing of position and inhalations of carbon dioxide, as well as the guarded use of narcotics, will minimize the predisposition to pulmonary complications. In multiple stage procedures usually the second operation may be performed any time after about two weeks, although the delay may have to be considerably longer. The cecostomy tube is to be removed when the fecal current follows unhampered the designed course. After obstructive resection, the bowel held in the three-bladed clamp will usually separate by necrosis between the fifth and ninth day, and at this point the clamp is removed. Two curved clamps are applied to the spur the second week after double-barreled colostomy and when tightened daily usually require about five to seven days to cause complete destruction of the spur. The colostomy opening will then gradually decrease in size and generally close spontaneously, but a surgical closure may be effected after all evidence of inflammation has subsided and the tissue has become sufficiently strong to hold sutures.

PROGNOSIS

While a great many factors influence the prognosis of colonic cancer, successful removal of a cancer is followed by freedom from recurrence more often in the colon than elsewhere in the gastrointestinal tract. Colonic cancer metastasizes to the glands slowly. As shown in Table 28, 34 per cent of the right colonic cancers and 31 per cent of the left colonic cancers showed glandular involvement in resected specimens. This is in sharp contradistinction to the 68 per cent of rectal cancers which show glandular involvement. The average of five year cures following removal of right colonic cancers with glandular involvement was estimated at 39 per cent, while for those without nodal involvement the average was 66 per cent. In the left half of the colon, five year cures averaged 29 per cent with nodal involvement and 56 per cent when the glands were not invaded.

Table 28.—Results of Treatment of Colonic Cancer

	With nodal involvement, percentage	Without nodal involvement, percentage
Right half:		
Incidence	34	
Five year cures	39	66
Left half:		
Incidence	31	
Five year cures	29	56

Age has long been recognized as playing an important role in the activity of malignant lesions. The resistance of youthful tissue, powerful in the face of acute fulminating disease, only serves to fan the flame of a relatively torpid neoplasm. The atrophic change in lymphatic structures incident to age decreases their efficiency to such an extent that malignant dissemination is retarded and the disease is thereby held in check.

TABLE 29.—THE INFLUENCE OF GRADE OF MALIGNANCY AND GLANDULAR INVOLVEMENT ON PROGNOSIS

	Grade 1, percentage	Grade 2, percentage	Grade 3, percentage	Grade 4, percentage
Cancer with glandular involvement (387 cases):				
Incidence	9	51	28	12
Five year cures	44	34	13	15
Cancer without glandular involvement (466 cases):				
Incidence	16	62	16	6
Five year cures	69	56	49	37

TABLE 30.—THE RELATION BETWEEN THE GRADE OF MALIGNANCY AND THE FIVE YEAR CURES IN REGARD TO THE HALF OF THE COLON INVOLVED

	Grade 1, percentage	Grade 2, percentage	Grade 3, percentage	Grade 4, percentage
Right half:				
Incidence	10	53	21	10
Five year cures	68	60	48	37
Left half:				
Incidence	13	67	16	4
Five year cures	63	51	30	18

In the heavy-set, robust or obese patient, other things being equal, the prognosis, regarding immediate operative mortality as well as ultimate curability, is unfavorable as contrasted with that of the wiry, sthenic patient. The degree of malignant change in a tumor, as judged by Broders' classification, is of vital significance. Obviously, the higher the grade of malignancy, the more rapid the dissemination, with the result that fewer patients fulfil the criteria of operability and many more succumb to recurrence. The relation of the grade of malignant disease to local glandular involvement found at operation and to ultimate curability gives proof of the value of Broders' contribution in the determination of prognosis.

MORTALITY

Statistics on operative mortality for malignant disease of the colon vary for the different segments involved. Age, coincident debilitating disease, duration of symptoms and the presence of obstruction—acute, subacute or chronic—all have an important bearing in the individual case. The earlier figures were discouraging, but recent data have compared favorably with those for the more radical surgical measures elsewhere in the gastrointestinal tract.

In 1922 Rankin reported a series of 150 resections of the right half of the colon with an operative mortality of less than 12 per cent, while during the three years prior to 1933 operation on the right half of the colon by a two stage procedure resulted in 60 aseptic ileocolostomies with only 4 deaths, a mortality of 6.6 per cent. In a study of 333 resections of the left half of the colon reported in 1926, the mortality was 16.2 per cent. In this group all types of operative procedure had been used, and it was found that the mortality following primary anastomosis was prohibitive. Exteriorization showed a mortality of 12.6 per cent, while it carried an incidence of recurrence in the abdominal wall of 12 per cent. By obstructive resection, the very satisfactory figure of 7.6 per cent was obtained in a series of 52 cases.

Mortality figures and operability curves both influence end-results directly. The prognosis following resection of the lower part of the gastrointestinal tract in our hands may be illustrated by a survey of 453 cases of cancer in this location, shown in Table 31.

Table 31.—Results of Resection

	Total cases	Dead	Cured	Percentage cured
Right half	187	81	106	57.6
Left half	266	139	127	47.7
	453	220	233	52.6

Thus it will be seen that cancer of the right half of the colon gives a prognosis of 57.6 per cent for five year cure, a figure 10 per cent better than that for the left half, which was 47.7 per cent. A glance at Table 31 indicates that malignant change in the lower part of the gastrointestinal tract on both the right and the left side tends to be of low grade, nearly two-thirds of the right colonic growths and three-fourths of the left colonic growths falling in grades 1 and 2, with an average of 52.6 per cent of five year cures for the whole colon for cancer of all grades.

The statement that the prognosis of cancer of the lower part of the gastrointestinal tract after radical removal compares favorably with the best prognostic statistics for cancer elsewhere in the body seems difficult to controvert.

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CHAPTER XXXIV

CANCER OF THE RECTUM AND RECTOSIGMOID

Cancer of the anus, rectum and rectosigmoid is relatively frequent. Four per cent of all cancers in the human body are in this region. However, 80 per cent of intestinal cancers are in the rectum and rectosigmoid. This means they are easy to diagnose; yet, nearly half of all the cancers of this region are overlooked until nearly one year after symptoms pointing to trouble have appeared. For this there are several reasons: First of all, too much pain has been given to patients in examination of the rectum, and most persons believe the procedure very uncomfortable and painful and delay examination for months. If the medical profession would learn to examine the rectum with little discomfort, which is easily done, in the course of time the public would learn that they are not going to be abused when the rectum is examined, and patients would reach the physician probably five months earlier, on the average, than they do now. If the public and the medical profession would stop the use of rectal suppositories, which have never been of any value in the treatment of any rectal condition, another three months would probably be saved. If patients were properly examined when they reach the physician—a digital, an anoscopic and a proctoscopic examination made—another three to five months would be saved. It is unfortunate that many members of the medical profession believe that a negative report from a barium enema rules out cancer of the rectum. This is true only for cancer which has constricted the rectum and is probably beyond hope. Prior to that cancer is not seen with the x-ray. An examination of stools revealing amebiasis means more delay. Digital, anoscopic and sigmoidoscopic examination can be done in five minutes and will reveal all cancers below 10 inches, with very little discomfort to the patient if the physician will use proper skill and care in inserting the finger or the instrument, after using an anesthetic lubricant in the anal canal.

CANCER OF THE RECTUM

Cancers of the rectum are comparatively late in metastasizing and are more amenable to treatment than cancers in many other parts of the body. If seen early—that is, within six months of their origin—about 80 per cent can be cured. However, as they are usually seen by the surgeon about one year from the date of their beginning, on the average, nearly half are beyond hope and of the other half about one-half can be given a five year cure by radical operation. Most important, therefore, are the education of the public to seek early examination and the education of the medical profession properly to examine the patient. In addition, the proper management of colostomy is a vital factor. When properly managed it produces a very little handicap, and the patient can be made perfectly clean, comfortable and happy. The frequent reference in the literature to the "social isolation" of colostomy patients indicates that this knowledge is badly needed. The proper management of colostomy is simple and easy. Further on in this article it will be described in detail.

Sex.—Cancer of the rectum and rectosigmoid is seen oftener in males than females in the proportion of about 3 to 2.

Age.—Ten per cent of rectal and rectosigmoid cancer occurs in patients under forty. Another 20 per cent occurs between forty and fifty, and 10 per cent occurs between seventy and ninety. This leaves 60 per cent of all cancers of this region in the two decades from fifty to seventy, the number in the decade from fifty to sixty slightly exceeding that in the decade from sixty to seventy.

No age is exempt from cancer in this region, though it is rare before thirty. In a series of 450 cases I have seen 5 boys with rectal cancer, their ages being seven, fourteen, seventeen, nineteen and twenty-three. There is no record in the literature of cancer in this region being cured in a patient under twenty.

Pathology.—Cancer of the rectum arising in the mucosa is of the columnar cell variety or adenocarcinoma. Cancer in the anal margin or the anal canal is epithelioma or squamous cell carcinoma. A clear distinction must be made between a cancer of this type and the ordinary type of columnar cell carcinoma, which in its development may go downward and involve the anal canal and grow out through the anus.

Carcinoma of the rectum in its early stages is a limited and local disease and commences from a raised nodule of atypical columnar epithelium on a mass of epithelial hyperplasia, an adenoma or papilloma, which soon shows submucous infiltration. It begins as a benign lesion, but most authorities agree that all polypoid growths of the mucosa should be considered precancerous. Ulcers, anorectal fistulas, hemorrhoids and other chronic inflammatory lesions when subjected to continuous irritation may undergo malignant changes. Carcinoma may be engrafted on diverticulitis or arise in postoperative scars. It is unusual, however, for carcinoma to develop in hemorrhoids.

The grade of malignancy if not of particular importance in treatment, but is very important in prognosis. Broders[2] classified malignancy in four groups, according to differentiation and mitosis. He said the more nearly the cell approaches the embryonic and undifferentiated type, the more malignant the tumor. Tumors in which about three-fourths or more of the cells are differentiated should be classed as grade 1; those in which differentiation ranges from 75 to 50 per cent, as grade 2; those in which differentiation ranges from 50 to 25 per cent, as grade 3, and those in which differentiation is 25 per cent or less, as grade 4.

The following résumé of the pathology of rectal cancer is condensed from the work of Miles.[8]

Carcinoma in the rectum and rectosigmoid is adenocarcinoma. There are three clinical varieties, differing in physicial characteristics and degree of malignancy, *viz.*, the papilliferous, the common adenoid and the colloid. The papilliferous type resembles an ordinary simple papilloma, extends rapidly on the surface and soon involves the whole circumference of the bowel. Owing to the exuberance of the growth, the lumen of the bowel becomes obstructed before infiltration of the muscular coat has progressed to any marked degree. Consequently, the growth is not particularly malignant and seldom gives rise to extramural metastases unless it has been in existence for a considerable time.

The great majority of cancers of the rectum are of the common adenoid type. Usually, the surface of the growth is a flattened tumor which increases in size in all directions and, although at first freely movable on the muscular coat, soon becomes adherent to it. This occurs, probably, within a few months. As the growth increases, surface ulceration occurs, and bleeding begins. As more of the circumference of the bowel becomes involved, the ulcer deepens and assumes a crater-like form, with nodular, everted and indurated edges. The growth commonly involves the entire circumference of the gut in from twelve to eighteen months. The colloid or mucoid type of carcinoma is merely a degenerative stage of this variety.

The papilliferous type is the least malignant of the three; the colloid type is the most malignant and practically always recurs, while the common adenoid type usually occupies a middle ground as regards malignancy.

Cancer of the rectum may spread in any of three distinct ways:

1. **Directly Through Continuity of Tissue.**—This takes place in two direction, *viz.*, on the mucous surface of the bowel progressively from its entire margin and through the thickness of the bowel wall. The marginal increase is generally greater and more rapid in the transverse direction than along the longitudinal axis of the bowel. Not uncommonly nearly the whole circumference of the ampulla has been invaded while the extent of the growth longitudinally is less than 2 inches.

Direct extension through the muscular coat of the bowel appears to be slow. When the bowel wall has been penetrated, the growth invades the perirectal fat, through which it extends to the fascia propria of the rectum. The fascia propria is not usually invaded until the growth has existed long enough for more than three-quarters of the circumference of the ampulla to have been encompassed. Only after penetration of the fascia propria can invasion of neighboring structures, such as the sacrum, uterus or vagina, prostate and bladder, take place; and it would appear that involvement of adjacent structures by direct extension does not occur until the expiration of at least a year after the first appearance of objective symptoms. Therefore, the mode of spread through continuity of tissue is comparatively slow, and direct invasion of neighboring structures does not take place until the growth in the rectum has involved the greater part of the circumference of the bowel.

2. **By Way of the Venous System.**—There is no doubt that cancer cells sometimes penetrate into the interior of small veins and, becoming detached, are carried in the blood stream. Actual invasion of a venous radicle is occasionally seen in miscroscopic sections of carcinomatous tumors. As the rectal veins belong to the portal system, cancer cells penetrating them are carried straight to the liver. The metastasis thus produced by an embolus of cancer cells is single and is usually situated in the middle of the right lobe of the liver. Fortunately, dissemination by the veins is rare, so that in practice the possibility can be disregarded.

3. **By Means of the Lymphatic System.**—Infinitely more important is the dissemination of cancer cells through the lymphatic channels, and a knowledge of the lymphatic system is essential to the performance of any radical operation for cancer.

Anatomists describe the rectal lymphatic vessels in three groups, intramural, intermediary and extramural.

1. The intramural lymphatic vessels are contained in the wall of the rectum and consist of two distinct networks, one in the submucous tissue

and the other between the muscular layers. The two networks communicate freely with one another by means of short radial channels which pass through the circular muscular coat.

2. The intermediary lymphatic system consists of two parts, a subserous network in the portion of the rectum covered by peritoneum and a lymph sinus situated between the external muscular coat and the perirectal fat in that part of the rectum which does not possess a peritoneal investment.

3. The extramural lymphatic system is the most important of the three. The collecting stems from the lymph sinus form an extensive plexus and enter into relation with the anorectal glands of Gerota, which are scattered over the surface of the rectum among the branches of the superior hemorrhoidal vessels. The efferents from this plexus and from the anorectal glands pass to their ultimate destination in three directions, downward, laterally and upward.

From clinical as well as histologic findings it may be concluded that the intramural spread of cancer of the rectum is always comparatively trivial. These observations lead to the belief that detached cancer cells pass through the bowel wall somewhat rapidly by means of the intramural lymphatic system and, gaining the external lymphatic vessels, give rise to extramural metastases scattered over a fairly wide area long before the muscular coat has been penetrated by direct extension of the growth.

Cancer cells, having passed through the submucous and the intermuscular lymphatic systems, gain access either to the subserous network or to the lymph sinus. Lodged in the subserous network, they may give rise to plaques in the peritoneal covering of the bowel; when, however, they enter the lymph sinus, they soon involve the extramural lymphatic system.

The direction in which the cells travel is largely influenced by the direction of the current in the lymphatic vessels which have been invaded. It must be remembered, however, that the path by which the cells advance is not controlled entirely by anatomic considerations. Thus, it may happen that cancer cells derived from a growth in the rectum, wherever situated, may traverse the lymphatic vessels in a downward, lateral or upward direction or in all three directions simultaneously. During the transit, their progress may be arrested at any point in the region traversed by the lymphatic vessels and lead to the formation of nodules. The various tissues through which the extramural lymphatic vessels pass, therefore, are prone to metastatic deposit, which is either macroscopic or microscopic. Whenever a visible metastasis exists, other metastases, which cannot be recognized without the aid of the microscope, also exist along the lymphatic channel at points more distant from the seat of the primary growth.

The extramural paths may be considered in three divisions, if it is remembered that communications exist between them.

Zone of Downward Spread.—The structures comprised in this zone are the perianal skin, the ischiorectal fat and the external sphincter muscle. Owing to the free intercommunication between the lymphatic vessels of those structures and the efferents from the rectum, it is easy to understand how the progress of a detached cancer cell may be arrested at any point in that extensive network. It is apparent also that even an exhaustive microscopic examination of the structures aforementioned might fail to detect such isolated cancer cells. Nevertheless, the presence of minute masses of cancer cells have been revealed in microscopic sections often enough to establish beyond doubt the fact that these structures are liable to invasion during the process of dissemination.

Zone of Lateral Spread.—This area embraces structures whose lymphatic vessels enter into relation with the extensive lymphatic network between the levatores ani and the pelvic fascia; these structures are the levator ani muscles, the coccygei, the pelvic peritoneum, the prostate gland, the base of the bladder, the cervix uteri and the base of the left broad ligament and the internal iliac glands.

The levatores ani are sometimes the seat of metastases and are exceedingly prone to invasion by cancer cells, which gain access to the extramural lymphatic vessels before the deep infiltration of the primary growth has had time to penetrate the muscular coat of the bowel, and they should, in all cases, be completely removed when a cancerous rectus muscle is excised.

Zone of Upward Spread.—The tissues of this zone are the retrorectal (lowermost mesocolic) glands, the pelvic mesocolon in its entirety, the paracolic glands, the glands situated at the bifurcation of the left iliac artery and the median lumbar (aortic) glands. Since the majority of the efferent lymphatic vessels, which form the intramural lymphatic system, either pass through or terminate in the structures contained in this zone, it follows that these structures constitute the principal paths by which cancer cells spread from primary growths in the rectum. In fact, these are the most important of all the routes of spread. Either macroscopic or microscopic metastases are found scattered throughout the zone in practically all cases of cancer of the rectum, even when the growth is in an early stage.

The pelvic mesocolon throughout its extent is particularly liable to invasion. So often, indeed, it is the seat of metastatic deposit that the removal of the whole of this structure in every case of operable cancer of the rectum is just as important as thorough clearance of the axilla in cases of breast cancer.

Diagnosis.—Cancer of the rectum and rectosigmoid can be easily diagnosed in a few minutes in 100 per cent of cases by digital, anoscopic and sigmoidoscopic examination. It is rare that barium enema and *x*-ray examination are required for diagnosis at the rectosigmoid junction. However, for a lesion above this point the barium enema and *x*-ray study, if properly done with double contrast, will nearly always show the lesion.

Digital Examination.—About 90 per cent of all rectal cancers can be felt with the finger. This does not mean that a casual and superficial digital examination will suffice, but a careful, properly conducted digital examination, with the patient in the left lateral position so that the knuckles can be turned toward the patient's back and the anus pushed up toward the coccyx, will enable the examiner to feel the tumor. The characteristic of malignancy is induration. An indurated lump felt in the rectum, especially one with a raised and everted edge, is almost always malignant. If a growth is situated above the reach of the finger it still may sometimes be felt by bimanual examination, the finger feeling a lump through the rectal wall in a higher loop.

Submucous thickening, which evidences submucous spread, may be felt digitally above or below a rectal carcinoma, or involvement of the regional lymph nodes in the mesorectum may be felt as small oval swellings.

The cervix uteri and the prostate should be identified and their relation to the tumor noted. An estimate of operability can usually be made by digital examination, by noting whether the tumor is fixed, its size and whether it is attached to other vital organs, such as the vagina, prostate and bladder, or posteriorly to the sacrum. If the growth is in the last 2 or 3 inches of the rectum it can be seen through an anoscope, preferably with the patient in the inverted posture.

Sigmoidoscopic Examination.—The inverted posture (Hanes position) should always be used for sigmoidoscopic examination. It can be used on any ordinary table, if the physician has no special table for the purpose, by placing a stool 1 foot high at the head of the table and a pillow on it to support the elbows. With the patient in this position it is rarely necessary to use the pneumatic bulb, which is a dangerous procedure, especially in cases of malignant growths, because perforation may be caused. The patient should be prepared by warm water enema, and the operator should be equipped with a suction tube and long alligator forceps and cotton sponges to clear the field. The sigmoidoscope should always be passed by sight, the obturator being removed immediately after passing through the sphincter. The raised indurated edge of a carcinoma of the rectum has such a characteristic appearance that it can scarcely be mistaken. Through the sigmoidoscope the operator will note the size of the tumor and how much of the circumference of the bowel is involved, and if possible the instrument should be passed beyond the tumor and the gut examined as high as possible. Multiple malignant tumors in this region probably occur in 5 per cent of the cases. A benign polyp or two may be found.

When the tumor is above the reach of the examining finger, considerable information as to the fixity of the growth can be elicited with the sigmoidoscope by holding the outer end of the instrument lightly in the fingers and gently pushing the growth. Whether it is fixed or movable can usually be determined by this method.

A biopsy specimen should always be taken for examination to corroborate the clinical diagnosis. This can be done easily and quickly without pain with a biopsy forceps. Many rectal biopsy forceps, however, take too large a bite, and I believe the Chevalier Jackson bronchoscopic forceps,* which takes a $\frac{1}{8}$ inch specimen, is the best. The specimen should be taken from the margin of the growth, because the grade of malignancy is more accurately noted at the margin than on the surface of the growth. The small wound made by the biopsy forceps should be cauterized at once with the electrocautery.

Early diagnosis of cancer of the rectum and rectosigmoid is of the highest importance, and the responsibility of this early diagnosis usually falls on the general practitioner. Therefore, all practitioners of general medicine should be trained to examine the rectum carefully. Sigmoidoscopic examination should be done in general examinations, because the cavity contains considerable disease—at least as much as, if not more than, any other—and there is no reason why it should be overlooked while every other cavity is carefully examined. A general examination without careful examination of the rectum up to 10 inches is not a complete examination.

Symptoms.—Cancer of the rectum and rectosigmoid is a silent growth, which usually causes no symptoms until three or four months or more have passed. Any change in bowel habit or sensation should cause the physician to make a careful examination. Even slight irritation or change in the character or frequency of the bowel movements from the previous normal should excite suspicion. If the lesion is at the rectosigmoid junction, not uncommonly there is rapidly increasing constipation, followed rather early by obstruction. In such cases it is of vital importance that no barium be given by mouth. If the lesion is not discovered by the sigmoidoscopic examination, an *x*-ray examination with barium enema should be done; this will show the constriction. Barium above the constriction may cause a partial obstruction to become complete. In fact, it is my opinion that all gastrointestinal *x*-ray series should be begun by the barium enema and not by the barium meal.

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* Made by Pilling & Co., of Philadelphia.

If blood appears in the stools it should never be considered to come from hemorrhoids until a lesion higher up has been ruled out. One of the saddest things one has to contend with is late cancer for which an operation for hemorrhoids had been done a few months or weeks before. This is frequent.

When the growth has gone on to partial obstruction, colicky pains and distention in the abdomen are usual, and in the thin patient peristaltic waves will probably be seen.

Of late years rectal cancer has been discovered earlier than before, because of considerable public health propaganda and better teaching of medical students. But much remains to be done, in education of both the public and the profession, if the patients are to be seen by the surgeon early enough to be cured.

Another strong argument for routine sigmoidoscopic examination is that many benign lesions will be found, such as small polyps (adenomas), which can easily be removed with the cautery and subsequent cancer probably avoided. After removal of a lesion of this sort the patient should be watched carefully at six month intervals to prevent recurrence or to discover the formation of subsequent growths.

Treatment.—All the factors present in a given case must be considered in deciding the proper treatment in that case. In general it may be said that the widest possible removal surgically is the best treatment of cancer, and cancer of the region of the rectum and sigmoid is not an exception. The age, sex, weight and general condition of the patient must be considered. The extent and location of the growth, the amount of fixation and obstruction, the presence or absence of metastasis or other disease and the grade of malignancy are the most important factors. Discriminating judgment, gained only by experience, must be used if the best interests of the patient are to be conserved. With the help of the internist many patients who would otherwise be deemed inoperable by reason of bad general condition, due to partial obstruction with its attendant toxemia, interference with digestion and nutrition, dehydration, secondary anemia and associated chronic diseases, such as diabetes and cardiovascular and renal disorders, may be rehabilitated to a degree warranting radical operation.

The best results in the treatment of cancer of the rectum and rectosigmoid are obtained by *radical operation*. Most authorities agree that *radiotherapy* should be used only as a preoperative or postoperative adjunct to surgical measures, for inoperable growths or sometimes for highly malignant cancers (graded high 3 or 4), for which recurrence after operation is the rule. These highly malignant growths are, fortunately, often highly radiosensitive. But even for these, radical operation offers the best chance of cure, if combined with preoperative and postoperative radiotherapy.

Three types of operation are now in general use, abdominoperineal resection, or perineoabdominal resection, in one stage; posterior resection preceded by colostomy, and abdominoperineal resection in two stages.

Few surgeons will disagree with the statement that the combined abdominoperineal resection, or the combined perineoabdominal resection, should be done whenever possible. The abdominoperineal resection in one stage as originated by Miles is being used by the majority of surgeons doing this work. Miles has proved that a much smaller percentage of recurrences follow this operation, in which the lower part of the sigmoid and the sigmoid mesentery are entirely removed, than follow posterior resection, in which the dangerous tissues of the mesosigmoid cannot be removed. If the primary mortality of abdominoperineal resection could be reduced to that of posterior resection following preliminary colostomy, all surgeons would agree that the more radical procedure should be used. This end is now in sight, for a series of 300 abdominoperineal resections with a primary mortality of 7.5 per cent has been reported. This was accomplished by more careful preoperative preparation, with special reference to decompression, transfusion and anesthesia. The two stage combined excision has no advantage over the one stage procedure if the patient is properly prepared and, in fact, has certain disadvantages in the risk of septic complications, which are not met in the one stage procedure.

Many modifications of these procedures have been made by different surgeons, and the particular procedure in any given case is a matter for decision by the individual surgeon.

Miles,[7] Jones,[4] Lahey and Cattell,[5] Gabriel,[3] Lockhart-Mummery[6] and others have given the technic of the various operations, together with statistics on operability, mortality and cures.

For results of radiotherapy the reader is referred to the work of Binkley.[1]

Final determination of the operability of these growths cannot be made until the abdomen is opened and explored, the local growth palpated and the liver examined. Sometimes growths which seem operable from digital and sigmoidoscopic examination will be found inoperable after the abdomen is opened, and growths which seem from the examination from below to be inoperable will often be found operable. The question of what to do when metastases to the liver and distant glands are found is one which taxes the good judgment of the surgeon. I believe that whenever the local growth is removable it should be removed, even though considerable metastatic deposition is found in the liver. Metastases will grow more slowly after the local growth is removed, and the patient will have a much more comfortable existence while he lives. When it is not possible to remove the local growth, a double-barreled colostomy should always be done, unless the disease has progressed to the point where life expectancy is very short. Sidetracking of the fecal stream gives the patient much more comfort than he could otherwise enjoy. The removal of the local growth under these circumstances is justified if the patient can be given six months of comfort. After such palliative colostomy deep roentgen therapy and the application of radium are often valuable palliative procedures.

CARCINOMA OF THE ANUS

Pathology.—Carcinoma arising at the anus or in the anal canal is of the squamous cell type or epithelium. It must be differentiated from columnar cell carcinoma arising in the mucosa above and growing downward through the anal canal. Epithelioma of the anus is comparatively rare, there being only from 3 to 5 per cent of rectal carcinoma due to this. It may occur at any age, and men are slightly more prone to it than women. It may arise on a preëxisting fistula, or a fistula may develop secondary to the epithelioma. A chronic anal ulcer with much induration of the margins may undergo malignant change.

An ulcer having a raised, warty appearance and with characteristic induration, as felt between the fingers or with the forefinger in the rectum, particularly when it has a hard base, is probably epithelioma. Symptoms vary with the situation of the growth, and pain is a marked symptom when the ulceration is in the anal canal and within the grasp of the sphincter. There will be some bleeding and some discharge. The inguinal glands require careful palpation, for they are frequently involved. If affected they are hard to the touch, and the prognosis is bad, but not hopeless.

Diagnosis.—The differential diagnosis is between epithelioma, simple papilloma, primary chancre and tuberculosis ulceration. A biopsy specimen should be taken for microscopic examination.

Treatment.—Radiotherapy or surgical intervention or both are indicated. A small local growth at the anal margin may be treated best by irradiation. If progress is not satisfactory and the growth is thus proved to be of a radioresistant type, a radical operation should be carried out immediately. Moderately advanced or more advanced growths, with deep ulcers in the anal canal, should be removed by radical operation, preceded by a double-barreled colostomy. These growths caused so much pain that colostomy is essential. A wide perineal excision of the rectum with the electrocautery or the diathermy knife should be done, and the resection should be wide. Such an operation together with radiotherapy will sometimes cure these lesions, but the outlook is grave. For any inguinal glandular development, excision with the radio knife or electrocautery should be done.

COLOSTOMY

To secure the largest percentage of five year cures of cancer of the rectum and sigmoid it is necessary to leave the patient with an abdominal colostomy opening and remove radically the distal part of the sigmoid, rectum and anus together with the mesosigmoid, retrorectal and ischiorectal structures which carry the lymphatic vessels of the three zones of spread, upward, downward and lateral.

It is not necessary here to review the arguments in favor of operations devised to save the anal musculature and normal sphincter control or of those procedures which leave the patient with a sacral or perineal anus without control. Thus far none of these procedures has shown as high a percentage of five year cures as combined abdominoperineal resection. These procedures have been motivated by a desire to save the patient from the "social isolation" of the "malodorous colostomy," so frequently mentioned in the literature on cancer of the rectum. Many physicians and almost all nurses feel that they would rather die than live with a colostomy opening; and this is due to the fact that even yet the large majority of patients who have undergone colostomy are wearing rubber bags or other gadgets which necessarily have a foul odor, although the *modern management of colostomy* which enables these patients to be clean, comfortable and happy and to carry on their usual social, business and professional engagements was worked out ten years ago and reported in 1932.[10]

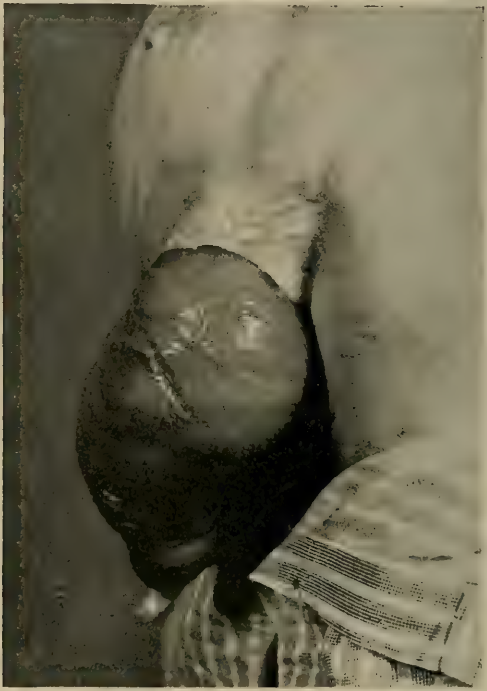

Fig. 165.—An unusually large prolapse after a double-barreled colostomy.

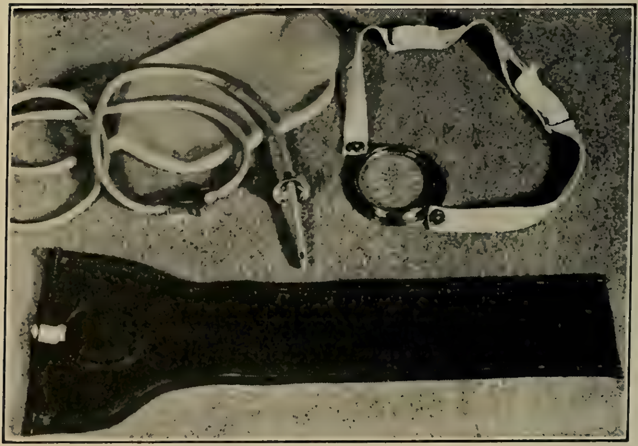

Fig. 166.—Apparatus for irrigating colon through colostomy opening.

It is essential that the colostomy be properly performed and in a proper location. Time-honored loop colostomy should never be done except for temporary use and subsequent closure, because too much mucosa is exposed and hernia is frequent. If a double-barreled colostomy is done, the procedure advised by Sistrunk[1] should be followed, the entire abdominal wall being sutured for at least 1 inch between the proximal and distal segments. This effectually prevents hernia and keeps feces from entering the distal segment.

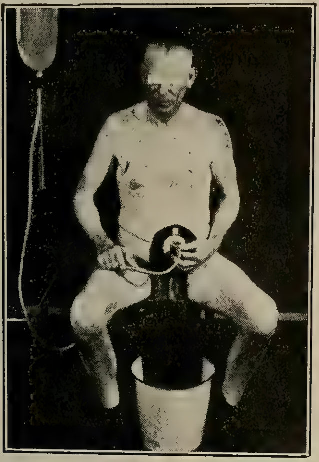

Fig. 167.—Patient filling the colon with physiologic solution of sodium chloride.

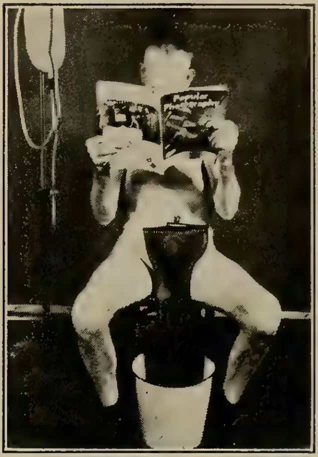

Fig. 168.—Patient expelling the enema.

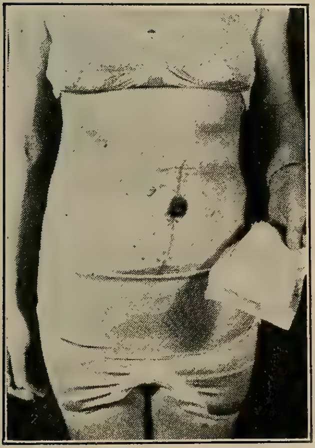

Fig. 169.—The colostomy dressing (gauze pad and glycerin-treated paper).

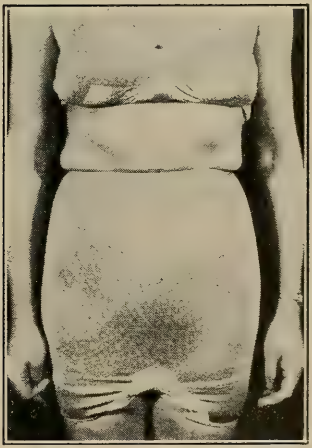

Fig. 170.—Two-way stretch garment drawn up over dressing.

The opening should be placed at or near the midline and close to the umbilicus. If placed in the inguinal region it is difficult to keep the dressing in position.

The gut should extend no farther than the surface of the skin, for protruding mucosa is disagreeable. No redundant loop of gut should be left in the abdomen, for it will prolapse (Fig. 165). A stoma 1 inch in diameter with no protruding mucosa should be formed.

Management.—Emptying the colon at regular intervals by enemas of physiologic solution of sodium chloride is the essential of proper postcolostomy care. To empty the colon completely it must first be completely filled with water, which necessitates apparatus to prevent the discharge of the enema until the colon is full. Such an apparatus* is shown in figure 166. The metal ring is placed over the colostomy opening, and the belt holds it snugly against the skin; the hole in the side of the wide rubber discharge tube is placed over the flange on the metal ring; the colon tube is inserted about 3 inches, and the edge of the metal funnel through which the tube passes is held snugly against the skin to prevent regurgitation. Figures 167 and 168 show the apparatus in use, and figures 169 and 170 show the gauze pad dressing covered by a sheet of glycerin-treated parchment paper and the elastic girdle. Women wear a two way stretch garment or a corset with a zipper and can dress as usual. Men wear a 6 or 8 inch elastic belt.

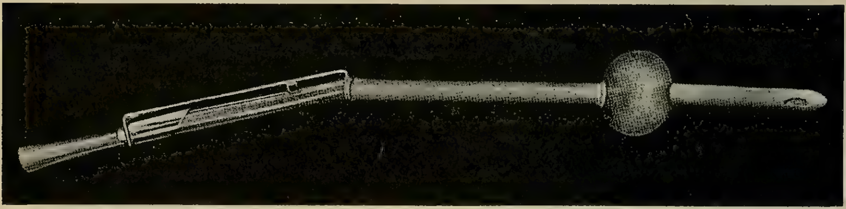

Fig. 171.—Colojector, which may be used instead of the apparatus shown in figure 166 and the enema expelled into a basin.

Managed in this way, two-thirds of the patients stay clean for forty-eight hours; a few use the seventy-two hour interval, and the rest prefer to irrigate the colon each twenty-four hours. The entire operation requires less than one hour and in many cases only thirty to forty minutes. No rubber dam or oiled silk is permitted to be worn between the gauze pad and the belt. A fresh piece of glycerin-treated paper is used each day.

Managed in this way, the colostomy opening is only a slight handicap and does not interfere with social engagements, sports, hard labor, business or professional pursuits. I have never had a patient refuse colostomy after talking with one or two patients who have been taught the proper management.

If a patient cannot afford the apparatus shown, my colojector* (Fig. 171) will keep the water from being expelled until the colon is filled and it can then be passed out into a basin. This is less convenient but equally efficient.

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* Supplied by John F. Greer Company, 4010 Broadway, Oakland, Calif.

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CHAPTER XXXV

OTHER DISEASES OF THE RECTUM

MELANOSIS COLI

This condition, a brown or black pigmentation of the tunica propria of the mucous membrane of the lower part of the bowel, is not properly classified as a disease, for so far as is known it has no pathologic significance. Bockus, Willard and Bauk[2] in 1933 made the first comprehensive study of the condition based on routine examination of living patients. They found an incidence of 2.7 per cent in a series of 960 office patients, but an incidence of 5.1 per cent in patients with definite colon stasis and a history of long-continued use of cathartics.

On sigmoidoscopic examination the mucosa is seen to be light brown, dark brown or black, either in patches or uniformly over the entire surface of the mucosa. The deepest pigmentation is in the rectum, diminishing from below upward and rarely involving the entire colon. There is no inflammatory or ulcerative factor, and if such is seen it is entirely independent of the melanosis.

Many theories have been advanced as to the source of the pigment and as to the process of its deposition in the mucous membrane. I have never seen melanosis coli in a patient who was not a habitual user of cascara or another anthracene cathartic and am in accord with Buie,[3] who said: "I believe that this pigment is obtained either directly from elements within laxative agents or from the products which develop as a result of the action of these chemicals on the intestinal contents." Bartle[1] first indicated cascara as the cause of melanosis coli in 1928.

Treatment.—The treatment should be directed to the cure of constipation and the withdrawal of cathartics. When this is accomplished, the pigmentation will usually disappear in from six to twelve months.

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HEMORRHOIDS

When man in the course of evolution stepped down from his arboreal habitat and assumed his erect carriage, he became subject to hemorrhoids, for not only is the rectum one of the regions where junction of the portal and caval venous systems occurs, but the absence of valves in a vein piercing the rectal wall predisposes the distal end to varicosities.

The superior hemorrhoidal veins anastomose freely in the submucosa of the rectal wall as well as with the inferior hemorrhoidal veins at the pectinate line. The superior veins forming the superior or internal hemorrhoidal plexus drain into the portal system by way of the inferior mesenteric plexus, while the middle and inferior hemorrhoidal veins forming the inferior or external hemorrhoidal plexus drain into the hypogastric and internal pudendal veins, respectively. Thus with two plexuses of venous sinuses one finds varicosities causing two types of hemorrhoids, internal and external.

Internal hemorrhoids appear as soft vascular tumors covered by mucosa or columnar epithelium arising from just above the pectinate or dentate line, and are usually found in three areas: right anterior, right posterior and left posterior, or lateral. They may vary in size from only a slight bulging of the mucosa found on anoscopic examination to large prolapsing tumors which require manual replacement after each defecation.

External hemorrhoids are varicosities of the external or inferior venous plexus, covered by skin or stratified squamous epithelium. These are also called skin tags or tabs. They appear as soft tags of redundant skin at the anal margin, and the venous constituent appears only on straining.

Mixed or internal-external hemorrhoids are a combination of the internal and the external variety, being a continuous tumefaction originating above the pectinate line and extending as one mass to the skin. They are composed of venous channels covered at the various levels by mucosa, anal lining and skin.

Symptoms of hemorrhoids vary with the condition. Small internal ones may give no symptoms and be found only on examination. Internal hemorrhoids may bleed, when the history given is of bright painless bleeding with defecation, the blood usually coating the stool and staining the water in the bowl. The appearance of blood is usually intermittent. If internal hemorrhoids prolapse enough so that they remain outside the anal canal—more often the case with the internal-external type—the clothing is stained with blood owing to its abrading action. Lastly, when a thrombotic hemorrhoid ruptures through the covering epithelium bleeding occurs. If the lesion is internal, the bleeding occurs with defecation; if external, it is not necessarily associated with stool passage. In any case, with the history of even slight bleeding and the finding of a hemorrhoidal area which is the apparent source, sigmoidoscopic examination should be done to rule out a coëxisting new growth in the lower 10 inches of the bowel.

The history of pain is elicited in the presence of thrombosis of either internal or external hemorrhoids or the internal-external variety. Prolapse is found in prolapsing internal or internal-external lesions and either reduces itself spontaneously or requires manual replacement after defecation, depending on the degree of protrusion.

Constipation appears when internal hemorrhoids are large enough to encroach on the lumen of the outlet, causing the patient to strain, particularly in starting the movement.

Itching and irritation are present with external tags or prolapsing internal and internal-external lesions, with which cleanliness is difficult to achieve and moisture accumulates in the folds, causing maceration of the skin.

The diagnosis of hemorrhoids is usually made by inspection only, internal ones not being palpable except when they are thrombosed. External lesions may be seen by merely retracting the buttocks. The internal type is seen on anoscopic examination, with the anoscope so placed that its distal end is at the pectinate line. An internal hemorrhoid is covered by mucosa unless it has been prolapsing, when, by apparent protective reaction on the part of the body, modified squamous epithelium grows up from the anal lining as a coating cover the hemorrhoid or the columnar epithelium through metaplasia is transformed into a type of squamous epithelium.

This reaction appears to protect the body from continued loss of blood due to erosion of the mucosa. The bleeding of hemorrhoids originates from the tiny vessels of the mucosa and not from the hemorrhoidal plexuses themselves, although the amount of bleeding may be considerable.

Thrombosis may occur in any type of hemorrhoid. In the external type, owing either to a sudden strain or to neighboring infection, the wall of the vein is ruptured; bleeding occurs under the skin, and clotting forms a dark blue, painful, exquisitely tender lump at the anal margin. Thrombosis of internal hemorrhoids produces a firm, tender, palpable lump beneath the mucosa.

Treatment.—Internal hemorrhoids, if small and not prolapsing, may be treated by the injection method—that is, a sclerosing solution may be injected at intervals until they are shrunken. Either a 5 per cent solution of quinine urea hydrochloride in physiologic solution of sodium chloride or a 5 per cent solution of phenol in a vegetable oil may be used for this purpose. (A note of warning: Mineral oil should never be injected, because it is not absorbed and causes a foreign body reaction.) All three hemorrhoids may be treated at one sitting and retreated at weekly intervals, providing the induration has subsided each time. The needle tip is inserted under the mucosa and enough solution injected to distend the hemorrhoid and erase the folds but not enough to blanch it, lest a slough occur.

Prolapsing internal and internal-external hemorrhoids require surgical removal by one of the technics available in any textbook on surgery.

External thrombotic hemorrhoids should be excised during local anesthesia, an elliptic incision being used, with dissection of all clots and connective tissue so that the skin edges come into nice apposition without sutures. If an incision and expression of only one clot is done, the discomfort usually continues about as long as if nothing had been done.

External hemorrhoids or skin tags may be excised during local anesthesia. These should never be treated with a sclerosing solution because of subsequent sloughing.

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LYMPHOPATHIA VENEREUM

Lymphopathia venereum, until recently known as lymphogranuloma inguinale, is infectious, of venereal origin in most instances and due to a filtrable virus. In the male, the initial lesion is followed by suppurative inguinal adenitis and rarely stricture of the rectum, whereas in the female, after the initial lesion stricture of the rectum is characteristic and is followed by abscesses and fistulas. To the proctologist the rectal manifestations are of most interest.

By far the greatest incidence of rectal involvement is found in the Negress. The more frequent occurrence of stricture in Negroes is probably due to their fibroplastic diathesis.

The initial lesion in the female is found on the fourchet, on the cervix or in the posterior fornix and usually passes unnoticed. About two weeks elapse before further spread of the infection takes place. Then the first rectal changes occur. The route of spread is thought to be through the lymphatic vessels of the vaginal fornices and cervix, which drain posteriorly into the network of channels surrounding the rectum, explaining the typical site of rectal manifestations.

In the male the lymph drainage system to the rectum originates in the posterior part of the urethra and prostate, whereas the drainage from the head and shaft of the penis leads to the inguinal glands.

The history given by the patient is often of a bearing-down sensation. Progressive constipation is present in each case of marked constriction. As the constriction progresses, the patient takes more cathartics, so that the stools are liquid and contain blood and pus. When the involvement is advanced the history of frequent soiling with blood, pus and feces is typical. Generalized symptoms, such as anorexia, loss of weight and fatigue, are frequently present.

On digital examination the findings vary with the extent and duration of the infection. At first the mucosa of the lower 2 or 3 inches of the rectum feels firm and coarsely granular. As the stricture itself develops it becomes evident as a firm, unyielding constriction, located most frequently about 2 inches from the anus. It may be diaphragmatic or tubular—that is, extending over a considerable length of the rectum—but in all cases it completely encircles the lumen. Care should be taken not to force the examining finger into the stricture, because of the bleeding which occurs and the possibility of perforating the bowel. On proctoscopic examination the stricture is evident and the mucosa found to be ulcerated and bleeding, with pus and blood mixed with the stool.

The most reliable laboratory test is the Frei test. This consists of intradermal injection into the patient's arm of antigen prepared from the purulent discharge from a patient known to have the inguinal lymphadenitic form of the disease. A positive reaction consists of the appearance of a hard red papule in from forty-eight to seventy-two hours. A control injection of tissue from normal glands should be used. This test, although not 100 per cent specific, is of great assistance in diagnosis.

The differential diagnosis between lymphopathia venereum and granuloma inguinale is made by microscopic section, in which the latter disease shows the characteristic Donovan bodies.

Treatment.—The sulfonamides have produced the most promising results. Sulfathiazole, sulfadiazine and sulfanilamide in the order named have proven most effective although sodium sulfanilyl sulfanilate and the less absorbable compounds sulfaguanidine and succinylsulfathiazole have also been used. Most authorities start with a large dose followed by a maintenance dose for a few weeks with rest periods of several weeks betwen courses of therapy, i.e., sulfathiazole 1.5 gm t.i.d. for two weeks, 1.0 gm t.i.d. for three weeks followed by a rest period of three weeks expecting a response in perhaps thirty weeks total; sulfadiazine 6.0 gm the first day, 3.0 gm daily for twenty days; sulfanilamide 20 grains q.i.d. for two to five days, 10 to 15 grains q.i.d. for a month followed by a rest period of several weeks; succinylsulfathiazole 15 gm daily over a period of weeks. Penicillin has yet to be proven efficacious.

Surgical intervention is indicated in the presence of marked constrictions not amenable to chemotherapy.

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CHAPTER XXXVI

ANEMIAS OF GASTROINTESTINAL ORIGIN

The gastrointestinal tract is implicated in diseases of the blood-forming organs, both primarily, in the production and absorption of the precursors of the blood cells and their components, and secondarily, as a result of a disease of the hemopoietic system.

Of the known substances which influence the growth and maturation of the red blood cells, for the purposes of this chapter protein, iron and "liver extract" may be considered.

DIGESTION AND ABSORPTION OF IRON

The exact mechanism of the digestion and absorption of iron is not known. The body may use metallic iron (*e. g.*, ferrum reductum) and produce adequate amounts of hemoglobin when this is apparently the primary source of iron. The hydrochloric acid in the stomach probably plays a part in dissolving the iron, and patients with achlorhydria do not absorb this metal as well as do normal persons.[2] This appears to be one phase of the circle of events which make up the syndrome of so-called idiopathic hypochromic microcytic anemia of middle-aged women. An excessive blood loss (menorrhagia) depletes the body of iron and the achlorhydria or hypochlorhydria which characterizes the disease[20] prevents adequate preparation and absorption of the iron of the food.[42] After gastrectomy, during the first two years, iron-deficiency anemia is common.

Some and possibly most of the absorption takes place in the stomach and duodenum. There is no doubt, however, that absorption occurs in other places, and the colon appears to play some part. The most profound iron-deficiency anemias occur in the presence of neoplastic lesions of the colon, especially the cecum and the ascending section. The extremely low color index, often 0.5 or less, appears to be out of proportion to any hemorrhage that may be taking place. Excessive mucin may inhibit or delay the absorption of iron.[29]

Iron is believed to be absorbed in the ferrous state. There is some evidence that ferrous salts, when taken by mouth, are more efficient in stimulating hemoglobin formation than other forms.[27] Metallic iron may be converted into the chloride or the sulfide as a first step, and later into other forms in organic combination. Hemoglobin itself, when taken by mouth, does not act as a source of iron for blood formation, and its various components find their way to the rectum unabsorbed. The final processes in the manufacture of hemoglobin take place in the bone marrow.

Of the iron taken by mouth, only a small portion is absorbed. The bulk appears in the stools, which are discolored a greenish black or black.

Iron (endogenous) is conserved by the body, and but for the loss during menstruation, the adult could get along with an intake of available iron of 5 to 10 mg. per day.[18] The distribution of hemoglobin in corpuscles, rather than in free solution, enables the body to localize the corpuscle destruction (in the spleen) and deliver the products to the liver without loss.

The iron released on cell destruction may be reused or stored (hemosiderin) in the spleen or liver. The pigment component reappears in bile. In the presence of biliary fistula, with loss of bile from the body, severe anemia may develop.[1] This may be remedied by the ingestion of bile. The absorption of iron appears to be influenced by bile, and in some patients the use of desiccated bile with each dose of iron stimulates rapid regeneration of hemoglobin.[46]

IRON-DEFICIENCY ANEMIAS

While failure to digest adequately the iron-containing foods (because of achlorhydria), combined with hemorrhage, accounts for the iron deficiency of hypochromic microcytic anemias, other forms result from failure to absorb the iron. In the presence of some types of chronic vomiting or diarrhea,[37] the loss of food appears to be a primary, although not the only, factor.

In the presence of chronic diseases of the throat or esophagus, dysphagia, with deficient ingestion of food, may result in inadequate food and iron intake. In some patients with chronic hypochromic microcytic anemia, practically all of them women, dysphagia appears to be a complication. The cause of this Kelly[38]-Paterson[47] or Vinson-Plummer syndrome is not evident. The lesion may be anatomic (web formation) or spastic.[50] In some it is said to be psychic in origin, but it is difficult to see why this peculiar response should appear in so many different persons. The symptoms may be avoided by some patients by lying on the stomach while eating (sea lion fashion).

With carcinoma or other neoplasms of the stomach the decrease in secreting surface may be reflected in the failure to absorb iron properly or to secrete the hemopoietic "enzyme."

While deficient intake of iron because of poor or improper food is not common in adults, it may appear in infants fed on cow's milk for periods longer than one year. It appears earlier and is more severe in those infants who, because born of anemic mothers, have a deficient iron reserve.[49] Nausea and vomiting (pregnancy) or perverted appetite, unwise diet or anorexia may play a part in the production of iron deficiency from defective intake. These factors may be contributory to the production of chlorosis.

Besides diets manifestly deficient in protein or iron, some foods appear to predispose to anemia. Goat's milk anemia is of this type. Children fed on goat's milk have an anemia which has some features of the hemolytic type.[24] Favism, from the ingestion of Vicia faba beans, may be accompanied by a rapidly developing hemolytic type of anemia with marked jaundice. In the presence of gross vitamin B deficiency, loss of appetite or a disturbance in intestinal metabolism may influence hemoglobin production. Certain forms of phosphorus in the gastrointestinal tract may prevent the absorption of iron by the formation of nonabsorbable compounds. Conversely, a prolonged high iron intake (medication) may upset phosphorus metabolism (*e. g.*, in rickets).

With hemorrhage from the gastrointestinal tract an iron-deficiency anemia of the hypochromic microcytic type develops. The source of bleeding may be varicose bloodvessels in the pharynx, esophagus, stomach or any part of the intestine or colon. The blood in the stools is likely to be black when the hemorrhage is in the stomach or duodenum and bright red when it is in the colon. The varicosities may be associated with obstructive lesions, as in cirrhosis of the liver or splenomegaly. This type of lesion is encountered in Banti's disease. Occasionally a patient has bleeding from hemangiomas in the gastrointestinal tract. The occurrence may be familial (hereditary hemorrhagic telangiectasia).[22] The diagnosis is often made only by exclusion, but the presence of such a lesion may be suspected if there are many hemangiomas on the skin or in the mouth and pharynx.

Ulcer is a common source of bleeding. Gastric and duodenal lesions appear to be the most common; less frequent sources are ulcers in the intestines, colon or esophagus. Gastric hemorrhage is usually present when there is diaphragmatic hernia.[48] Parasites of the hookworm type give rise to blood loss.[15]

With the development of severe anemia, hydrochloric acid secretion in the stomach may be diminished or absent, only to return in some cases with the use of massive doses of iron.[12] With microcytic hypochromic anemia of childhood, gross reduction in acid secretion may be noted.[16]

In the presence of chlorosis, the gastroscopic view of the stomach usually shows diffuse gastric atrophy, but sometimes the stomach appears normal or shows atrophic, pearly areas.[13] With other iron-deficiency anemias there may be gastric atrophy with granular slate-colored areas (syphilis), pallor (hypochromic anemias), increased mucus secretion with abolition or decrease in the number of folds (chronic nephritis with azotemia), various degrees of atrophy of the mucous membrane (hepatic cirrhosis with alcoholic neuritis), absence of fundic rugae with visible veins (sprue, tumor formation, sometimes cancer), a normal or slightly atrophic, pale fragile appearance (leukemia, lymphopathy, splenomegaly), no abnormality or total atrophy (severe anemia with marked fever), punctate or gross hemorrhagic areas, with areas of pearly degeneration (purpuric diseases) or ulcers or dilated vessels (posthemorrhagic conditions).

In diseases associated with deficiency in the blood-clotting mechanism or with capillary fragility, multiple bleeding areas appear in the gastrointestinal tract. In some forms of congestion there is blood loss into the lumen by diapedesis or abnormal capillary permeability. In the thrombocytopenic purpuras and in the nonthrombocytopenic, allergic and capillary fragility forms the mechanism appears to be similar. Hemorrhage of this type, involving the stomach or intestinal wall, is usually accompanied, clinically, by local or diffuse pain, distention, failure of peristalsis, nausea and vomiting.

Bleeding is noted occasionally when multiple polyps or diverticula are present.

Symptoms of Iron Deficiency.—The symptoms may be limited to ease of fatigue. Pallor may or may not be present, depending on the state of the cutaneous capillaries, the thickness of the skin and the amount of pigmentation. Other symptoms, such as dyspnea, palpitation, nausea, vomiting, edema, headache and dizziness, are dependent on the strength of the heart muscle. With myocardial insufficiency, these symptoms appear in proportion to the heart failure.

One group of symptoms seems to be related to iron deficiency: This includes defects in epithelial structures (fissures at corners of mouth, glossitis and spoon-shaped fingernails, or koilonychia), and some physicians attribute the dysphagia to this cause, as it may disappear in some patients with a high iron intake, even in the absence of anemia.[26]

The blood picture varies with the rate of developments of the anemia. With the acute hemorrhagic form, a neutrophilitic leukocytosis develops within twenty-four hours, with an increase in the number of blood platelets. The inflow of fluid, to bring the blood volume back to normal, causes the red blood cells to swell. Contraction of the spleen releases stored red blood cells into the circulation. Within four days, evidence of new red blood cells appears in the peripheral blood (reticulocytosis). Cells that are made rapidly pass through the megaloblast stage quickly and are therefore small. Rapid passage through the normoblast stages results in less hemoglobin formation in the cells. Pale, small corpuscles result (hypochromic microcytic anemia). With return of the rate to normal, or with increase in the rate of availability of the nutritive components, the cell size and color return to normal.

When the bleeding process continues (bleeding gastric ulcer, telangiectasia, hemorrhoids, etc.) the leukocytosis and evidence of abnormal hyperplastic development disappear. A hypochromic microcytic anemia is present, but there is little reticulocytosis. Pencil-shaped red blood cells appear in the blood.

Under certain conditions, the rate of corpuscle production becomes fast enough to bring the count within the range of normal. The hemoglobin concentration may remain low, unless the availability of iron is greatly increased. This is the picture of the iron-deficiency anemia of chronic hemorrhage or defective iron availability.

Treatment of Iron-Deficiency Anemia.—The problem is to make iron available in large doses. The most common remedies are: reduced iron, 0.5 Gm. (7½ grains), three times a day after meals; ferrous sulfate, 0.2 to 0.32 Gm. (3 to 5 grains), three times a day after meals; ferric ammonium citrate, 4 cubic centimeters of a 50 per cent solution three times a day, and Blaud's pills, 3 to 5 pills, three times a day after meals. In some patients, 4 grains of desiccated bile may aid the absorption of the iron or possibly supply additional nutritive factors. It is seldom necessary or wise to give the iron intravenously or intramuscularly. If persistent vomiting makes oral medication impossible, green iron and ammonium citrate, 0.06 Gm. (1 grain) may be given daily by the intravenous route. A marked febrile or constitutional reaction or severe pain may make it necessary to discontinue this method of treatment. For those patients in whom constipation accompanies iron administration, vitamin B complex in the form of yeast or yeast extracts may be given. Chlorophyll-containing foods have some theoretic value.[45]

The more frequent the dose of iron, the more effective is the absorption.[4] Thus, small doses at hourly intervals may accomplish more than larger doses at three or four hour intervals. Other elements which go to form hemoglobin are apparently synthesized or absorbed during the process of digestion and converted through the intermediary of the nuclei of the erythroblasts into hemoglobin. If red blood cells do not mature, much of the pigment is not used, giving rise to bilirubin. It is possible that some of the jaundice with increased bilirubinemia of pernicious anemia has this origin. The hemoglobin of hemolyzed red blood cells is a contributing factor.

Perhaps the acid product of iron developed in the stomach is converted into another form in the less acid or alkaline duodenum. This may be the second step in the synthesis of the precursors of hemoglobin. However, some iron is absorbed, even in the absence of hydrochloric acid digestion, although the amount is greatly diminished. Hydrochloric acid may be administered with meals, 4 cubic centimeters in a glass of water, with the other food. This may relieve the symptom of fulness and may possibly influence iron digestion to a slight degree.

In the presence of hemorrhagic disease, blood transfusion may be necessary. Untreated or citrated blood may be used. In cases of capillary fragility, telangiectasia or bleeding varices, moccasin snake venom may be given subcutaneously in increasing doses from 0.3 to 1 cubic centimeter over long periods. Of the coagulants, fibrogen, thromboplastin, sodium citrate intravenously, coagulen, cephalin and similar substances may be tried. Pectin, 1 Gm. (15 grains) in capsules three times a day one-half to one hour before meals, is helpful in thrombocytopenic conditions.

Surgical intervention may be necessary for bleeding gastric or duodenal ulcers, intestinal hemorrhage or hemorrhoids. Leukemic ulcers of the stomach may occasionally respond to *x*-ray therapy directed at the general leukemic condition.

MACROCYTIC ANEMIA ASSOCIATED WITH INSUFFICIENCY OF "LIVER EXTRACT"

Normally, there is secreted in the stomach a substance, presumably an enzyme,[11] hemopoietin, which converts some element of the food (probably protein) into a material which when absorbed and stored in the liver, constitutes "liver extract." This substance supplies a material to the megaloblasts of the bone marrow which enables them to mature into normoblasts and ultimately into adult red blood cells. The longer a red blood cell is delayed at the megaloblast stage, the larger is the mature corpuscle which develops from it. Conversely, a predominance of large red blood cells, with a normal or high mean corpuscular hemoglobin concentration, suggests that there is a block in growth at the megaloblast stage and thus an insufficiency of available "liver extract."

In man, the intrinsic factor probably is secreted by glands in the pyloric region and the duodenum. If the stomach is removed, the body must depend on the decreased amount of the intrinsic factor secreted in the duodenum, and presumably on such stores of "liver extract" as may be present in the other organs. Under these conditions an iron-deficiency anemia frequently develops during the first year, but after eighteen months to two years a macrocytic anemia develops in those cases in which production of the intrinsic factor is inadequate. In some cases it appears as early as five months after the operation, whereas in some it may not appear for fifteen years.[44] It may appear after other destructive diseases, such as gastritis.

Macrocytic anemia may appear after gastroenterostomy, at times after eleven to twenty-eight years.[23] Total gastrectomy does not cause the blood picture of pernicious anemia or combined degeneration of the spinal cord, stomatitis or glossitis during a year in the rat, twelve years in the dog, three years in the pig and two and six-tenths years in the monkey.[9,35]

There is little contraindication to proper gastric surgical measures, since anemia, if it occurs, responds to adequate therapy.[36]

In pernicious anemia, the amount of intrinsic factor secreted is reduced.[32] This amount varies in different persons, so that some have enough to make sufficient "liver extract" to mature 3,000,000 or 4,000,000 red blood cells per cubic millimeter, whereas others can produce only 1,000,000 per cubic millimeter. Furthermore, there appear to be variations in each person, so that the amount of secretion may increase or decrease. This may be one factor in spontaneous remissions, although adequate food (the extrinsic factor) plays a part.

The total amount of fluid secreted in the stomach is reduced in patients with pernicious anemia. The average, under fasting conditions, is 20 cubic centimeters per hour during relapses and 46 cubic centimeters during induced remissions, as compared with 150 cubic centimeters for normal persons.[19] These patients never secrete hydrochloric acid, even during remissions.[39] This is probably a contributory factor in the finding of bacteria in unusual amounts in the gastrointestinal tract in such persons. The growth of bacteria is secondary to the gastric defect and not the primary cause of the anemia. The amounts of pepsin and rennin are also diminished.[30] It is possible that the few cases reported of "pernicious anemia" with free acid in the gastric contents have been, in reality, instances of cirrhosis of the liver or of other macrocytic anemias. Certainly achlorhydria is a symptom of all patients with neurologic involvement. In a number of patients with pernicious anemia on whom gastric analyses were made many years before the development of anemia no "free" acid was found. A significant feature is that other members of a patient's family may exhibit achlorhydria but no anemia. Some members may show other types of anemia.

The tendency to "anemia" appears more commonly in some families than in others. Of 377 patients with pernicious anemia, 27.3 per cent knew of cases of anemia in their immediate families, whereas of 536 patients without pernicious anemia only 9.1 per cent had anemic relatives. The gastrointestinal abnormalities of the pernicious anemia patients were only part of a group of characteristics (long ears, lantern jaws, bodily habitus, hair and eye color) which showed the constitutional predisposition to the disease.

The relation of the neurologic changes of pernicious anemia to the gastric dysfunction is not known. The sore tongue, with ultimate atrophy of the lingual papillae, may be associated, in the general process, with the atrophy of the gastric glands, but the lesions may be independent. The mechanism of macrocytic anemia in carcinoma of the stomach is similar to that of pernicious anemia.

In patients with sprue,[8] idiopathic steatorrhea[53] with intestinal stricture[17] or stenosis,[25] regional ulcerative ileitis, ileocolic fistula, chronic dysentery,[37] extensive intestinal anastomoses, carcinoma of the head of the pancreas or Dibothriocephalus anemia, the precursor of liver extract may be made normally, but the degree of absorption may be very limited. The ultimate results are an inadequate supply of "liver extract" to the megaloblasts in the bone marrow and a macrocytic anemia. Liver extract given by mouth may be ineffective for these patients, although they may respond to daily intramuscular injections.[11d] The deficient food factor appears to be an important element in tropical macrocytic anemia.[54]

In some patients with cirrhosis of the liver, a macrocytic anemia is present.[55] The mechanism in these persons is the failure to store the liver extract[19c] or possibly to elaborate the last stage in its manufacture.[21] The megaloblastic bone marrow[31] under these conditions and the improvement in the anemia with adequate dosage of liver extract[19c] show that the available maturing substance is inadequate.

With pernicious anemia the main macroscopic lesion is an atrophic thinning of all the coats of the body of the stomach, while grossly the pyloric area and duodenum appear normal.[40] These are areas, however, which are supposed to secrete the "intrinsic factor" or enzyme (hemopoietin) and which one would expect to be abnormal in the presence of pernicious anemia.[43] With the gastroscope, atrophy of the mucosa may be visible, with pearly areas and visible bloodvessels. Pseudotumors (localized edema?) may be present. Partial return to normal appearance follows remission in the disease.[10,13]

The cause of the gastric lesion of pernicious anemia is unknown. The achlorhydria is probably a congenital or constitutional factor and not a cause of the anemia. Of normal persons over forty years of age, 15 per cent show achlorhydria, and the incidence in older persons is higher.[7] Yet these persons do not have pernicious anemia, nor do the achlorhydric relatives of a patient with the disease have it. Deficient (vitamin B complex) diet given to animals may cause anacidity, and a prenatal or neonatal nutritional deficiency has been suggested as a cause of the gastric lesion of pernicious anemia.[51] A macrocytic anemia may develop in patients with benign adenomatous polyposis. The polyps, usually in the pyloric region, may be secondary in the patients in whom anemia develops to a primary pathologic process of the mucosa, which, in itself, may predispose to the anemia.[51] Carcinoma may exist with pernicious anemia,[14] and many patients kept alive by liver therapy reach the "carcinoma age" and undergo development of neoplastic growths.

Absorption appears to be defective in pernicious anemia.[28] Failure to absorb protein or a low blood protein level may cause macrocytic anemia.[6] The total bile secretion is increased during the relapse in pernicious anemia.[3]

In connection with the concept of "infected teeth" as a cause of anemia, 36 per cent of the pernicious anemia patients in my series had "bad" teeth (control group, 47 per cent), and 49.5 per cent had had all their teeth removed (control group, 37.2 per cent). The edentulous patients often had difficulty in chewing their food, leading at times to a limited diet. This added an additional factor in the anemia. Glossitis was noted by 73.3 per cent of the pernicious anemia patients and by only 7.8 per cent of the group without pernicious anemia. Of the first group, 69 per cent showed evidence of atrophy of the lingual papillae, while this was noted in only 2.7 per cent of the controls.

Symptoms of Macrocytic Anemia.—The symptoms of macrocytic anemia are, as a whole, similar to those of iron-deficiency anemia. In pernicious anemia neurologic symptoms may be added. There may be severe constipation from loss of sensation in the intestine and colon. There may be a long history of "indigestion." Loss of appetite appeared in 43.9 per cent of

580 cases of pernicious anemia in relapse, as compared with only 14.8 per cent of a similar group of patients without pernicious anemia. Constipation appeared in 54.3 per cent (36 per cent in the control group); diarrhea, in 26.5 per cent (5.5 per cent of controls). Of the pernicious anemia group, 62.6 per cent had symptoms referable to the stomach, as compared to 41.4 per cent of those without pernicious anemia. Of the former group, 87.1 per cent had tenderness over the gallbladder, as compared to 89.5 per cent of the latter group. Nausea and vomiting were experienced by 55 per cent of a series of patients with pernicious anemia, and a like number had abdominal discomfort from distention ("dyspepsia"). Upper abdominal pain unrelated to meals bothered 7 to 12 per cent, and 12.1 per cent (7.2 per cent in the control group) gave a history of transient jaundice other than that characteristic of the disease at some time. In one series[5] 53 per cent lost these symptoms after adequate antipernicious anemia therapy (liver or stomach), 38 per cent were improved and 9 per cent were not helped. When "iso-iodeikon" was administered, 31 per cent showed delayed absorption of the dye. Roentgenologic examination showed gallbladder dysfunction in 22.5 per cent. Bethell and Harrington concluded that persistence of gastrointestinal symptoms in persons suffering from pernicious anemia after remission has been induced strongly suggests the presence of gallbladder disease. Such patients do not respond at the normal rate to liver or stomach therapy.

In the presence of sprue, cirrhosis of the liver, Dibothriocephalus anemia, carcinoma of the stomach, carcinoma of the head of the pancreas, intestinal stricture or anastomoses and tropical anemias (macrocytic) the symptoms are characteristic of the underlying disease. Some patients with Dibothriocephalus anemia (macrocytic) have pernicious anemia and the tapeworm is an incidental or a precipitating factor. In others the tapeworm appears to have a toxic effect. The anemia may be relieved by liver therapy, even with the tapeworm *in situ*.[34]

Anemias associated with certain vitamin deficiencies have been noted. A macrocytic anemia sometimes appears with pellagra, and various types of anemia may appear with scurvy. Part of this may be due to hemorrhage, but often there is an element of bone marrow deficiency. In the presence of vitamin B complex deficiency, besides loss of appetite, deficient intestinal motility and defective absorption play a part in the development of a nutritional anemia.

In the macrocytic anemias, such as pernicious anemia, the red blood cell count is reduced proportionately more than the hemoglobin percentage, so that the color index is high. The mean corpuscular volume is usually above 100 cubic microns, and the mean corpuscular hemoglobin is normal or increased. The mean corpuscular hemoglobin concentration may be normal, decreased or increased, depending on the iron reserves in the body. The red blood cells in pernicious anemia tend to be oval, and have a wide range in diameter from very small to very large (3 to 13.5 microns). In sprue and cirrhosis of the liver and the related anemias, the cells are round and the range of size is wide, but in the direction of the large sizes, without microcytosis. Remission is accompanied by the appearance of reticulocytes in the peripheral circulation, in direct proportion to the number of megaloblasts whose growth has been inhibited in the bone marrow and in inverse proportion to the red blood cell count. After about two weeks the cells are delivered from the bone marrow in a mature state, and the red blood cell count increases. With the remission, the leukocytes and the platelets, which have been decreased in number, increase to normal. During remission the red blood cell size and shape return to practically normal, but change quickly when a relapse is beginning. A high color index (above 1) when the red blood cell count is near normal indicates an impending relapse due to insufficient liver or stomach therapy.

Treatment of the Macrocytic Hyperchromic Anemias.—The treatment of pernicious anemia and related hyperchromic macrocytic anemias consists in supplying adequate amounts of "liver extract." For patients who can absorb liver extract by mouth, the dose is 1 U.S.P. (oral) unit of liver extract daily. Desiccated stomach (ventriculin) may be given in doses of 10 to 40 Gm. daily, suspended in water or other cold fluids.[33] Cooked liver may be taken in doses of 250 Gm. daily or five to six times a week. Mixtures of liver and stomach are available, and in adequate doses are effective. For intramuscular injection, 1 U.S.P. (injectable) unit is given daily, or corresponding doses at longer intervals (*e. g.*, 14 units every two weeks). There is no harm in giving larger doses, and there is distinct therapeutic advantage when the blood count is very low. An intravenous preparation can be had, of which 20 cubic centimeters is given every four to five weeks. For those who cannot store liver extract (*e. g.*, those with liver disease) the intramuscular injections must be given daily or, at most, every two days. For diseases associated with hypermotility of the intestine (diarrhea), oral medication is usually inadequate. Hydrochloric acid is necessary only for those patients who have a feeling of heaviness after meals. As a rule, the gastrointestinal symptoms (except neurogenic constipation) disappear with the onset of the remission induced by liver extract or ventriculin. For tropical macrocytic anemia, yeast extracts, such as marmite or vegex, appear to be very beneficial.[52] These substances, as well as brewer's yeast, may be given in conjunction with iron or liver if the results produced by either one alone appear to be slower than expected.

Vitamin A deficiency in infants appears to be associated with a hemolytic type of anemia resembling Lederer's anemia. The anemia disappears when large doses of vitamin A are given.[41]

If as the red blood cell count increases the color index falls low enough to indicate an iron deficiency, iron may be added, just as in the treatment of hypochromic anemias.

For the neurologic complications, purposive exercises are indicated: For the feet, walking is the best exercise; for the hands, delicate work, as tying and untying knots in a piece of rope or string; for the bladder, emptying, by compression, at regular intervals. For the intestine, pituitrin may be given at intervals of two or three days, with interruptions to see if spontaneous movements follow. On theoretic grounds, a high intake of the known vitamins may be tried. For the sore tongue, 1 per cent silver nitrate may be applied locally to the sore spot. With adequate intake of liver extract or desiccated stomach no special diet, other than well balanced normal meals, is necessary. There appear to be theoretic grounds for including green vegetables.[45]

With any type of treatment, the aim is to keep the red blood cell count near 5,000,000 per cubic millimeter. As individual patients differ considerably in the amount of antianemia medication needed, frequent blood studies are a necessary part of the treatment.

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PART V

Dietary Concepts

CHAPTER XXXVII

THE DIETETIC CONCEPTS OF GASTROINTESTINAL DISEASE

INTRODUCTION

Special diets have been used widely in the treatment of various diseases of the gastrointestinal tract. Many of these were purely empiric and have proved valueless. Many were planned so carefully from the standpoint of the pathologic condition that a deficiency disease or at least a poor nutritive state developed.

The normal nutritive demands of the body must be met at all times, no matter what the disease. The food may have to be modified, from the standpoint of texture, consistency, quantity, individual constituents or energy value, but the essentials for good nutrition must never be omitted. Planning often demands much ingenuity, since the food habits, likes and dislikes of the really ill patient must be considered but not allowed so to affect the patient's food intake that his diet is incomplete.

NUTRITIVE REQUIREMENTS

Protein.—The normal nutritive requirements of an adult cannot be set absolutely, but the standards recommended by the Committee on Food and Nutrition of the National Research Council are proving satisfactory and workable (table 32). The first requirement in the diet is sufficient protein of good quality. One gram per kilogram of body weight with 50 per cent of the intake furnished by meat, milk and eggs—*i. e.*, biologically efficient protein—permits good maintenance, adds to the iron intake, allows variety in meal planning and is not too high a standard economically. Protein from sources such as cereals, legumes or vegetables, if used exclusively, as in some few cases of allergy, must be fed at a higher level. This standard allowance must be increased in the case of growth, as for the child or the pregnant woman; after periods of deficient intake, or when protein is lost through the kidneys, as in nephrosis, through oozing, as in extensive burns, or through withdrawal of large amounts of ascitic fluid.

Any marked decrease in protein intake, such as has been used in the treatment of chronic nephritis, should be made with greatest attention to the quality of the remaining protein and to the caloric needs.

Table 33, showing the approximate protein values of some common foodstuffs, can be used as a guide either in checking a patient's intake or in instruction as to dietary habits.

A daily allowance of 1 pint of milk, 2 eggs and 2½ ounces of meat, with a serving of some protein-rich food such as cheese or navy beans, insures an adequate intake of efficient proteins.

TABLE 32.—RECOMMENDED DAILY ALLOWANCES FOR SPECIFIC NUTRIENTS*
(Committee on Foods and Nutrition, National Research Council)

	Calories	Protein, Gm.	Calcium, Gm.	Iron, mg.	Vitamin A,‡ I.U.	Thiamin (B₁), mg.†	Ribo-flavin, mg.	Nicotinic acid, mg.	Ascorbic acid, mg.†	Vitamin D, I.U.
Man (70 Kg.)										
Moderately active	3,000	70	0.8	12	5,000	1.8	2.7	18	75	¶
Very active	4,500	..	..	..	..	2.3	3.3	23		
Sedentary	2,500	..	..	..	..	1.5	2.2	15		
Woman (56 Kg.)										
Moderately active	2,500	60	0.8	12	5,000	1.5	2.2	15	70	¶
Very active	3,000	..	..	..	..	1.8	2.7	18		
Sedentary	2,100	..	..	..	..	1.2	1.8	12		
Pregnancy (latter half)	2,500	85	1.5	15	6,000	1.8	2.5	18	100	400–800
Lactation	3,000	100	2.0	15	8,000	2.3	3.0	23	150	400–800
Children up to 12 years:										
Under 1 year§	100/Kg.	3–5/Kg.	1.0	6	1,500	0.4	0.6	4	30	400–800
1–3 years△	1,200	40	1.0	7	2,000	0.6	0.9	6	35	¶
4–6 years△	1,600	50	1.0	8	2,500	0.8	1.2	8	50	
7–9 years△	2,000	60	1.0	10	3,500	1.0	1.5	10	60	
10–12 years	2,500	70	1.0	12	4,500	1.2	1.8	12	75	
Children over 12 years:										
Girls, 13–15 years	2,800	80	1.3	15	5,000	1.4	2.0	14	80	¶
16–20 years	2,400	75	1.0	15	5,000	1.2	1.8	12	80	
Boys, 13–15 years	3,200	85	1.4	15	5,000	1.6	2.4	16	90	¶
16–20 years	3,800	100	1.4	15	6,000	2.0	3.0	20	100	

TABLE 33.—PROTEIN VALUES

Food	Amount	Measure	Approximate** protein value, Gm.
Milk	16 ounces	1 pint	15.0
Eggs	100 Gm.	2	13.4
Lean meat or fish	75 "	1 mod. serv.	15.0
Cheese	50 "	1 cube, 1¼ in.	15.0
Cottage cheese	75 "	¾ cup	15.0
Navy beans	225 "	1¼ cups	15.0
Enriched or whole wheat bread	160 "	6 slices	15.0

Energy Requirement.—The calorie-bearing foods, carbohydrates and fats, are essential in the normal diet. The energy intake must cover the energy output if normal weight is to be maintained. Its increase in case of under-weight and its decrease in case of over-weight without omitting nutritive essentials are frequent problems. The allowance of fat should be at a level which will not tax the fat-combusting ability of the body. The usual diet contains from two and one-half to four times as much carbohydrate as fat. When extra calories are needed, carbohydrates, though not as concentrated as fats, usually permit a more rapid and satisfactory gain and interfere less with appetite.

Measuring the Calories Required.—Calories required are usually estimated on the basis of energy output as related to activity, though age and sex also are factors. Twenty-five to thirty-five calories per kilogram of body weight is sufficient for the average adult. A basal level averaging 1,000 to 1,250 calories for a woman and 1,400 to 1,600 for a man, plus 50 per cent for activity, is another measure of this requirement. The caloric requirement on the basis of hours of sleep and of various types of activity also can be calculated. The patient's ability to maintain his average or satisfactory weight is the best index of an adequate caloric intake. The caloric intake of the adult population at all economic levels is for the most part adequate. The caloric requirements given in Table 32 also can be used as a guide.

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* Tentative goal toward which to aim in planning practical dietaries. This can be met by a good diet of natural foods. Such a diet will also provide other minerals and vitamins, the requirements for which are less well known.

† One mg. thiamin equals 333 I.U.; 1 mg. ascorbic acid equals 20 I.U.

‡ Requirements may be less if provided as vitamin A; greater if provided chiefly as the provitamin carotene.

§ Needs of infants increase from month to month. The amounts given are approximately those needed at six to eight months. The amounts of protein and calcium needed are less if derived from breast milk.

△ Allowances are based on needs for the middle year in each group (2, 5, 8, etc.) and for moderate activity.

¶ Vitamin D is undoubtedly necessary for older children and adults. When not available from sunshine, it should be provided probably up to the minimum amounts recommended for infants.

** Approximate values from Waller, Nutritive of Foods, Ann Arbor, Mich., George Wahr.

Essential Minerals.—Standards of intake for calcium, phosphorus and iron are included in the requirements set up by the National Research Council.

Studies establishing the iron requirement are still in progress, and data are still conflicting. Men have been kept in balance on intakes of 5 to 10 mg., but the level for women should be higher.

Information as to the function and requirement of other minerals, such as potassium, sodium, magnesium and so-called trace metals (manganese, copper, cobalt and aluminum) is still incomplete.

The normal average diet contains approximately 5 to 6 Gm. of potassium daily. This can be reduced by careful choice of food and methods of preparation to 1 to 2 Gm., but the diet is limited in variety and low in calcium and the vitamins. A diet low in potassium is used in the presence of Addison's disease or when insufficiency of the adrenal cortex seems likely, but a combination of a diet moderately low (3 to 3.5 Gm.) in potassium with a sodium intake of 10 Gm. or more daily in addition to any used with the food has proved more satisfactory. Potassium intake can be raised easily by choice of food.

The average intake of sodium chloride in food and as added salt is from 5 to 7 Gm. daily, but may be as high as 10 to 15 Gm. Diets can be planned to contain as little as 0.9 to 1 Gm., but these are monotonous and incomplete. An allowance of 2 to 5 Gm. of salt permits a much more satisfactory diet from all standpoints, and thirst is well controlled at this level, permitting moderate water restriction. Diets containing large amounts of sodium chloride, 7 to 10 Gm., are easily planned by addition of certain highly salted foods, such as cheese, ham and bacon, and additional sodium can be given as sodium chloride and sodium citrate in capsules or solution.

Controlled manipulation of minerals in the diet is being attempted for the first time, and much additional information is desirable. For insufficiency of the adrenal cortex, heat stroke, severe fevers, Simmonds' disease, surgical shock, Ménière's syndrome and infantile rickets, sodium and potassium may be or are known to be of importance.

Copper is accepted as essential in hemoglobin formation. Aluminum and manganese are found in many tissues and organs, and the latter is considered essential. Cobalt deficiency produces a definite disease in animals in New Zealand and Australia; its presence in foodstuffs and in the animal body in this country varies widely, and its essential nature is not yet established. Copper is found in minute amounts in many foodstuffs, especially milk, and in many times a contaminant from utensils. In many fruits and vegetables it is a contaminant from sprays, and it is also present in the soil. Aluminum is widespread in plant and animal tissues. It may be a constituent of foods, such as some baking powders, and some of it can be accounted for by the widespread use of aluminum cooking utensils. However, the amounts present are small and never prove toxic.

Analysis of raw and cooked fruits and vegetables at this institution showed from 0.002 to 0.12 mg. of copper per hundred grams and 0.002 mg. of aluminum per hundred grams, but no cobalt or manganese.

Acid-Base Residues.—The acid-base relations of the body as affected by food are little understood. Popular advertisements intimate that acidosis is a common complaint and alkalinizing the body the cure for many ills.

The classification of foodstuffs into acid- or base-producing residues has added to the confusion in the lay mind, since fruits and vegetables are base producing, while protein-rich foods, such as meat, eggs and cheese, in general tend to increase the acid radicals. To the latter group should be added cereals, because of their high phosphorus content, and milk should be listed as a basic residue food because of its relatively high calcium, potassium and sodium contents in relation to the phosphorus and sulfur.

In general, acid-residue foods increase urinary acidity and alkaline-residue foods reduce this. Prunes, prune plums and cranberries, though basic, are exceptions. Their acidifying effect is ascribed to the content of quinic and benzoic acids, which are conjugated to hippuric acid for excretion. Milk is an exception also, producing acid urine when used as the only food.

The reaction of the urine can be modified by choice of foods. A *p*H as low as 5 or as high as 8 can be reached. In the planning of the diet, excess acid or base is expressed as milliliters of normal acid or base per hundred grams of foodstuff. The normal average arrangement of food gives excess base to 20 to 40 milliliters. A diet containing more than 100 milliliters of excess base can be planned without the use of excessive quantities of any of the basic foods. On the other hand, a diet containing 25 milliliters of excess acid is palatable but somewhat limited in variety. If increase in urinary acidity is the end-point of the dietary change, addition of milk, prunes, prune juice and cranberries is effective and less tiresome to the patient.

Efforts at influencing the blood acid-base relation by means of diet have not been conclusive. Balance studies run at this institution over rather long experimental periods showed the retention of larger amounts of base on the high basic diet, but changes in *p*H, carbon dioxide-combining power and total base in the blood were slight and difficult to interpret.

Residue in the Diet.—It is pretty well established that habit and regularity of food intake in the production of a normal stool are as important as the bulk in the food itself. The ability of the cellulose to hold water, rather than just its bulk, is important in the production of a normal stool. The average requirement for residue is between 3.5 and 5 Gm. daily, which means a consumption of only 500 to 600 Gm. of residue-bearing foods, rather than the large quantities of raw fruits and vegetables or other cellulose-rich products which have been suggested.

Vitamins.—The importance of vitamins in maintaining a good nutritive state has assumed the character of a fad. Vitamin preparations are hailed as cure-alls. A sane attitude or even an intelligent attitude is difficult, because the knowledge of the number of vitamins, their function and their chemical structure is imperfect. It is increasingly evident that vitamins from natural sources, though possibly not as concentrated as in the synthetic products, contain important factors as yet unrecognized.

The vitamin requirements recommended by the Foods and Nutrition Committee of the National Research Foundation are given in Table 32.

Frank vitamin deficiency states, such as xerophthalmia, polyneuritis, scurvy and rickets, are easily recognized, but the so-called subclinical states are more difficult to identify. Diagnosis is complicated for the most part by the lack of simple laboratory methods to determine the level of the vitamin in the body, its rate of excretion or the degree of change. Many times the disappearance of certain symptoms when massive doses of vitamins are given is as much proof as one can obtain of a suspected deficiency.

Visual acuity has been used as a sign of *vitamin A* deficiency. Since the photometric test must be made under carefully controlled conditions by an adequately trained technician, its use is limited. As yet, reports of such examinations in relation to kidney stone formation, to infections of the upper part of the respiratory tract and even to some definitely recognized deficiency states have been unsatisfactory and conflicting.

Careful dietary histories and careful examination of the epithelium and of the eyes may help in deciding the question of vitamin A deficiency. Studies indicate that vitamin A is a preventive agent in infections of the upper part of the respiratory tract, but its importance in curing these same infections or in preventing kidney stone formation in man is open to question. Nevertheless, an adequate or liberal intake in forms which insure absorption would seem to be indicated whenever tissue healing or intact and healthy epithelial tissue is desired.

Patients with fat intolerance, with a fat loss in the stools up to 25 per cent or with biliary destruction are still able to absorb and utilize vitamin A. If liver damage is extensive, vitamin A deficiency may develop, and there is a possibility of loss due to renal permeability. Most frequently the deficiency symptoms appear because of inadequate intake.

Table 34 gives the amounts of food required for adequate vitamin A intake (5,000 I.U.).

TABLE 34.—VITAMIN A REQUIREMENTS

Food	Amount	I.U.
Eggs	2 (100 Gm.)	1,400
Milk	1 pint	528
Butter	1½ oz. (45 Gm.)	900
Leafy vegetable	200 Gm.	2,200

There are many stumbling blocks to recognition of subclinical deficiencies of *vitamin B complex.*

Anorexia and poor tonus along the gastrointestinal tract, as demonstrated by Cowgill in experimental animals, for example, responded quickly to vitamin B_1 therapy. However, it is difficult to show in the average adult patient with anorexia that vitamin B_1 brings about any improvement, for psychologic factors and habits of eating overshadow the return of appetite.

It is easier to demonstrate the response of the colon to vitamin B_1 or to the whole B complex. The water content of the stool approaches normal;

the number of movements is regulated, and the patient becomes free from minor gastrointestinal tract distress. With improvement in bowel tone, the patient shows improvement in appetite, but not the startling response of the experimental animal with frank deficiency.

Vitamin B_1 deficiency appears in certain pathologic conditions. Its tie-up with the pellagra of alcoholism is well established. Polyneuritis in pregnancy when there has been vomiting or a limited intake in amount and variety of food is recognized.

Polyneuritis or pellagra-like symptoms appear also with esophageal or pyloric obstruction, either before or soon after operation. A poor food intake for a long period and inability to retain the food explain this. Intravenous medication can well include thiamin chloride and ascorbic acid in such cases.

Recent studies have stressed the importance of vitamin B_6 in acrodynia, and the richest sources of this pigment are such commonly used fats as corn and cottonseed oil. Experimental animals respond to its use. As yet there are few cases on record of its successful clinical use.

Simple methods for showing the presence of any or all of the vitamin B complex in the blood stream, in any of the fluids of the body or in the excreta have not yet been developed.

Scurvy in adults is rather rare. Though vitamin C levels in the blood and the urinary excretion can be determined, it is not yet possible to set up criteria for subclinical deficiency. From 0.8 to 2 mg. per hundred cubic centimeters is the normal range for vitamin C in the blood, with a urinary excretion of 13 to 35 mg. Under the influence of massive doses of vitamin C, a saturation phenomenon appears, with the critical blood level at 1.3 to 1.4 mg. and almost total excretion of the test dose when saturation is complete.

The method used for blood determination is usually the Farmer-Abt microtitration of 0.2 to 0.3 milliliters of finger blood with 2.6 dichlorophenol-indophenol. The same dye is used for the determination in urine (Harris and Ray). The capillary resistance test does not seem as sensitive or as easy of interpretation.

Vitamin C levels in the blood are somewhat lower after operative procedures and are definitely lowered in the presence of elevated temperature or increased metabolism. Low levels are observed on entrance to the hospital in many patients without any recognizable symptoms of scurvy, and seem to be related largely to a poor intake.

Foods vary in vitamin C, and though raw fruits and vegetables are credited as being the best sources, nevertheless, the inclusion of liberal amounts of potatoes, customary in the midwest, helps insure an adequate intake. Milk, though containing a rather poor concentration, 0.3 to 2.5 mg. per hundred milliliters, adds an appreciable amount to the diet, since it is consumed liberally by many children and adults.

Table 35 gives the vitamin C contents of various foods, useful in planning a diet to furnish the 75 mg. necessary for the average adult.

TABLE 35.—VITAMIN C CONTENT

Food	Amount	Vitamin C, mg.
Milk	1 pint	7
Potatoes	150 Gm.	35
Fruit or green vegetables	100 Gm.	15
Citrus fruit	100 Gm.	40

Aside from its relation to rickets, the function of *vitamin D* is little understood. No figure has been set for the adult requirement except during pregnancy and lactation. Excessive doses prove toxic to experimental animals, but the range between a liberal dose and this excess is so wide that the problem does not seem immediate.

Vitamin D in normal and excessive doses has been suggested as curative or preventive for arthritis, hay fever, psoriasis, trichinosis and kidney stone formation, as well as many other conditions. Proof, however, is lacking. In cases of fracture its use combined with adequate calcium and phosphorus intake is well established.

Table 36 summarizes the normal dietary essentials in terms of common foodstuffs.

TABLE 36.—ESSENTIALS OF THE DAY'S FOOD FOR AVERAGE ADULT

Daily standard		Wt.,	Protein, 1 Gm. per kilo	Calcium 0.8 Gm.	Iron, 12 mg.	Vit. A, 5,000 I.U.	Thiamin, 1.5–2 mg.	Riboflavin, 2–3 mg.	Ascorbic acid, 75 mg.	Vit. D, 400–600 I.U.
Food Items	Measure	Gm.	Gm.	Gm.	Mg.	I.U.	Mg.	Mg.	Mg.	I.U.
Milk	1 pint	480	15	0.6	0.15	528	0.264	1.0	6.0	
Meat, fish or fowl	1 serving	75	15	..	3.1	50	0.17	0.23		
Eggs	2	100	15	0.06	2.9	1,400	0.15	0.33		
Cheese* . . .	1½″ cube	50	15	0.46	0.7	1,000	0.005	0.37		
Leafy vegetables .	2 servings	200	..	..	4.1	2,200	0.22	0.30	40.0	
Citrus fruits or tomatoes . .	1 serving	100	..	..	0.4	250	0.10	0.05	35.0	
Potatoes . . .	1 serving	150	..	..	1.3	75	0.18	0.06	35.0	
Fruits, all kinds .	1 serving	100	..	..	0.6	250	0.08	0.06	15.0	
Whole grain cereal and bread . .	3 servings	100	9.5	..	1.0	..	0.30	0.103		
Butter	1½ oz. 4 cubes	45	..	..	..	900				
Cod liver oil .	1 tsp.	..	..	..	..	..	..	..	..	Satisfied
Totals . .	. . . .		70	1.12	14.25	6,600	1.51	2.50	131.0	

* Satisfactory substitutes for cheese: lean pork, 1 serving; cooked navy beans, 1 cup; peanut butter, 3 tablespoons; milk, 1 pint; liver, 1 serving.

The list of foods in Table 36 does not call for an excessive outlay of money or for great ingenuity in planning. Meat, milk, eggs, cheese and legumes furnish adequate protein when used in moderate amounts. The use of two leafy vegetables daily and fruit twice possibly incurs some changes in the average family's meals. This table does emphasize the need for variety in foodstuffs. No one food is able to fulfil all requirements or to protect against deficiencies, but since few foods are valuable for only one factor, the more varied the intake, the greater the chance of meeting one's many requirements.

Calories are easily added to the diet and need be considered only as the other requirements are fulfilled. Sugar and so-called sweets, such as candy, jelly and syrup, are mainly pure forms with nothing but the calories and flavor as recommendation. Desserts such as cake, cookies, custards and ice cream may add not only calories but appreciable amounts of some of the essentials, but should not be used to the exclusion of fruits.

This table can be used as a guide either in checking the patient's intake or in teaching new food habits. Wide variety in types of food eaten is the best insurance against nutritive insufficiency.

High Vitamin Diet.—Addition of 1 pint of skim milk, 1 serving of a green vegetable and 1 pint of tomato or orange juice daily increases the intake of all the vitamins to a higher level without any great change in the total calories. If calories are needed, whole milk and special whole grain cereal preparations well fortified with the vitamin B complex can be used either as cereal or as bread.

THE GASTROINTESTINAL TRACT

In the preparation of food for absorption so that it can be utilized by the body, the motor and secretory activities of the gastrointestinal tract are most important and individually or together are capable of partial or complete failure. Also, inflammation, ulceration, infection, foreign bodies or malignant growths may interfere with the normal performance of duty.

The Stomach.—Secretion and motility in the stomach are affected by psychic factors. Foods by their individual components also are factors. Meat and particularly meat extractives are stimulants to gastric secretion and to bile formation; fats inhibit gastric secretion and motility but stimulate the contraction of the gallbladder. Carbohydrates are more or less inactive, except as they influence both the external and the internal secretion of the pancreas.

Condiments are considered adverse or at least irritating to the mucosa. Data as to this point hardly meet the present day standards of research, but the effect on the mucous membranes of the mouth and eye would lead one to suppose that the gastric mucosa would respond in the same way.

The amount, consistency and texture of food also affect gastric function. Small quantities and liquid and finely divided food pass out of the stomach more readily than large quantities and coarse food, and the secretion of acid is less.

The stomach can equalize temperatures quickly, but some scanty data recently compiled at this institution indicate that a marked change in the temperature of the food brings about temporary inhibition to secretion.

The whole tract is dependent on its parts and is affected by conditions in other parts of the body. Infections accompanied with high temperature depress secretion, motility and appetite. Malnutrition does likewise. Chronic infections with little temperature change but with pus formation, such as sinus infection and osteomyelitis, are characterized by poor appretite. Sore mouth, gastric distress and diarrhea are seen with pernicious anemia.

The average normal person takes a mixture of all kinds of food and is unconscious of all the many factors which affect its utilization and of the effect of the food and his habits on the body's ability to use this food. When, however, either the whole gastrointestinal tract or any part of it functions poorly because of abnormality within the tract itself or elsewhere in the body, then conditions must be made as favorable as possible for the utilization of food.

Food Habits.—In all dietary care of the gastrointestinal tract, regularity in food habits is necessary. This means regularity not only in the time of eating but in the amounts—that is, moderate amounts should be well spaced during the day so as to take care of the need for energy at all times, and similar amounts should be taken at similar times. In other words, breakfasts should be similar to breakfasts, lunches to lunches, etc. Fatigue, worry, confusion and hurry at mealtime must be avoided.

It must be impressed on the patient that mild or even severe gastric discomfort or strong dislike of a food does not mean that the body will fail to use it. On the contrary, unless the discomfort is such that the food actually comes up, the body will get the full benefit of all that actually reaches the mucous membranes of the intestine. Dislike of many foods or discomfort after eating, common complaints of the under-weight person, may be responsible for the under-weight by affecting the total intake of food, but these do not affect its utilization by the body.

Depressed Function.—When the secretory and motor abilities of the stomach are depressed, the comfort of the patient can be much increased by changes in the amount of food at each meal, with increase in the number of meals if necessary to insure an adequate intake of food; by changes in texture of the food; by decrease in the amount of fats, such as cream, butter or fat meats, and by liberal use of meat stock and meats as gastric stimulants.

For a soft or smooth diet with more frequent meals, two plans can be used. The first is the normal arrangement of food at the regular meal, with servings one-half or two-thirds normal size. Regular lunches are then given between breakfast and the noon meal, in the afternoon and before retiring. This procedure is followed by most institutions, since it is the most convenient.

The second plan is reduction in the number and variety of foods given at a meal, with division of the food into four or five meals for the day. This entails much more planning but sometimes insures a larger and more varied intake.

Distinctly bulky foods are omitted, but certain foods such as lettuce, grapefruit and orange sections are allowed to add interest to the meal.

The two plans follow:

THREE MEALS WITH LUNCHES

All servings are *one-half* to *two-thirds* the usual size.
The diet will contain:

1. Eggs (poached, soft boiled or scrambled), custards, cheese (cottage)
2. Broths, used freely
3. Chicken, fish, lean beef, lamb, veal, crisp bacon (meat must be ground or chopped unless tender)
4. Potatoes (baked or mashed), rice, macaroni, spaghetti, farina, cream of wheat, wheatena or sieved oatmeal
5. Vegetables (cooked except lettuce)
6. Fruits (cooked except ripe and canned pears, ripe bananas, orange and grapefruit); the juice of one orange or 1 glass tomato juice daily
7. At least 1 pint of milk daily (more if possible)
8. Bread (white) toast (used only when essential items are taken in the desired amount)
9. Butter, cream (in moderation)
10. Desserts: Ice cream, sherbets, plain jello, plain cake and cookies and custard desserts (bread, rice, tapioca or cornstarch pudding)
11. Fruits and vegetables, sieved or chopped if the patient complains of bulk
12. 1 teaspoon cod liver oil
13. Vitamin B complex daily

Avoid: Fried, raw, fat and spicy foods, rich desserts, nuts and cocoanut.

Suggested Menu

Breakfast	*Dinner*	*Supper*
Orange juice	Bouillon, saltines	Vegetable soups (met stock with mild vegetables)
Soft egg	Roast beef (small serving)	Crackers
Toast and butter	Mashed potato and butter	Lamb chop
Milk	Tomatoes	Peas
Coffee	Pear salad, no mayonnaise	Milk
	Milk	Applesauce or baked custard
	Ice cream	

10 A. M. *Lunch*	3 P. M. *Lunch*	9 P. M. *Lunch*
Milk	Chicken sandwich	Milk toast
Prune sauce and wafers	Cocoa	

FIVE MEALS

The diet will contain:

- Eggs, in any form except fried
- Cheese: Cottage cheese or other very mild cheese
- Meat: Lamb, roast beef, steak, chicken, fish, crisp bacon
- Milk: At least 1 pint daily
- Butter, cream and sugar (very moderate amounts)
- Cereal: Farina, cream of wheat, rice, oatmeal, cornflakes or prepared rice cereals
- White bread, toasted; macaroni or spaghetti, in moderation; crisp white crackers or saltines
- Fruits: Cooked or canned pears, peaches, apricots, applesauce, prunes (may include ripe peeled fresh pear, ripe banana, orange sections, grapefruit sections); no fruits which have seeds; the juice of at least one orange or 1 glass tomato juice daily
- Vegetables: No raw vegetable except lettuce; cooked string beans, peas, carrots, chopped spinach, asparagus, tomatoes, squash; *avoid* cabbage, onions, turnips, cauliflower, parsnips, corn (except sieved)
- Potatoes: White or sweet, well baked or mashed
- Soups: Meat broth
- Desserts: Plain puddings (rice, tapioca, bread or custard), jello, ice cream, sponge or angel food cake without icing, plain sugar cookies, no nuts, raisins, cocoanut, dates
- Coffee and tea, in moderation

1 teaspoon cod liver oil daily

Vitamin B complex concentrate daily.

Avoid: Fried foods, spices, vinegar, pie, pastry, all raw foods except orange juice, grapefruit juice, lettuce, orange sections, grapefruit sections, peeled ripe fresh pear or ripe banana.

Suggested Menu

Breakfast	12 *noon*	6 P. M.
Orange juice	Lamb chop	Chicken broth with rice
Cereal, cream and sugar	Peas	Broiled fish
Coffee	Sherbet	Tomatoes
	Milk	Baked apple

10 A. M. *Lunch*	3 P. M. *Lunch*	9 P. M *Lunch*
Soft egg	Beef broth	Chicken sandwich
Toast, jelly	Pear and cheese salad	Hot milk or cocoa
Cocoa	Cocoa	
	Wafers	

Increased Function.—When hyperacidity is pronounced, some control is possible through choice of food, and greater comfort can be assured the patient by control of quantity. Fatigue, strain, irregularity, etc., are particularly important in increasing discomfort.

Meat and meat extractives are used with a great deal of care, and milk and egg proteins, because of their ability to combine with the hydrochloric acid, are used instead. Fat can be used liberally because of its inhibitory action.

The presence of small amounts of food in the stomach at all times increases comfort, and small feedings prove less stimulating than large feedings. There seems to be little need for change in the texture of the food as long as the quantity is controlled. A suggested regimen follows:

THREE MEALS WITH LUNCHES

(Limited Meat—Increased Fat)

The fruits and vegetables should be cooked if the patient complains of bulk.
All servings will be one-half or two-thirds the normal size.
The diet will contain:

- Milk, 1 quart daily
- Eggs, in any form except fried (2 daily)
- Cheese: Cottage cheese or other very mild cheese
- Meat: Lamb, roast beef, steak, chicken, fish, crisp bacon (only one serving daily)
- Butter and cream, in liberal amounts
- Cereal: Farina, cream of wheat, rice, oatmeal, cornflakes or prepared rice cereals
- White bread, toasted; macaroni or spaghetti in moderation; crisp white crackers or saltines
- Fruits: Cooked or canned pears, peaches, apricots, applesauce, prunes (may include ripe peeled fresh pear, ripe banana, orange sections, grapefruit sections); no fruits which have seeds; the juice of at least one orange or 1 glass tomato juice daily
- Vegetables: No raw vegetable except lettuce; cooked string beans, peas, carrots, spinach, asparagus, beets, tomatoes, squash; *avoid* cabbage, onions, turnips, cauliflower, parsnips, corn (except sieved)
- Potatoes: White or sweet, well baked or mashed
- Soups: Cream soup, no meat broth
- Desserts: Plain puddings (rice, tapioca, bread or custard), jello, ice cream, sponge or angel food cake, without icing, plain sugar cookies; no nuts, raisins, cocoanut, dates
- Coffee and tea, in moderation.

Avoid: Fried foods, spices, vinegar, pie, pastry, all raw foods except orange juice, grapefruit juice, lettuce, orange sections, grapefruit sections, peeled ripe fresh pear or ripe banana.

Suggested Menu

Breakfast	*Dinner*	*Supper*
Orange juice	Cream soup, crackers	Creamed cottage cheese
Soft boiled egg	Roast beef	Baked potato and butter
Toast and butter	Mashed potatoes and butter	Toast and butter
Milk, half cream	Buttered peas	Canned peach salad, mayonnaise or whipped dressing
Coffee or tea	Milk	
	Sliced bananas with thin custard	Ice cream
10 A. M. *Lunch*	3 P. M. *Lunch*	9 P. M. *Lunch*
Eggnog or milk and cream	Chocolate milk Wafers	Milk, half cream

Gastric Rest.—Rest for the stomach may be of great benefit in many conditions which are likely to be of short duration and when the nutritive condition of the patient is good.

With acute infection with high temperature, for example, the patient is usually not interested in food, and his secretory ability is depressed. For gastritis also, freedom from activity seems beneficial.

Fluids, however, are necessary, leave the stomach rapidly and make little demand on it. The presence of dextrose or sucrose up to 10 per cent makes little difference but does protect the body against dehydration and acidosis.

Feedings at frequent intervals permit a more satisfactory total fluid intake, and the quantity at a single feeding can be small enough so that the patient will not feel distended. Studies on normal subjects indicate that up to 750 milliliters can be taken without any discomfort. The average bed patient finds 600 milliliters a pretty good load, while patients who are irrational or very uncomfortable will not take that much at a time. The amount and number of feedings must be handled from these various angles.

LIQUID DIET

Select diet from the following:

Milk, whole or skim
Buttermilk
Broth
Coffee
Tea
Grape juice
Orange juice
Lemonade
Canned fruit juice
Tomato juice
Plain jello
Sherberts
Ice cream

Suggested Menu

Breakfast	*Noon*	*Supper*
Fruit juice with dextrose	Broth	Broth
Cereal gruel	Fruit juice with dextrose	Fruit juice or tomato juice
Coffee or tea	Sherbet	Milk
Milk		
10 A. M.	3 P. M.	7 and 9 P. M.
Orange juice with sugar or other fruit juice	Fruit juice with dextrose or hot milk drink	Fruit juice with dextrose

Peptic Ulcer.—Dietary treatment of peptic ulcer is still handicapped by lack of knowledge of the etiology of the disease. Nevertheless, the dietary systems for the most part have assumed an etiologic factor in excess hydrochloric acid and have aimed at its neutralization with food or chemicals. But a dietary system consisting of hourly feedings of small quantities of milk and cream alternating with alkaline powders is incomplete from the nutritive standpoint. Supplements to the milk and cream feeding usually consist of bland foods, such as highly refined cereals, toast, eggs and cooked bland fruits, but the diet is still incomplete and monotonous.

Work with dogs with experimentally produced ulcer and with patients indicated that the texture of the food has only a slight influence on the healing time and that hemorrhage does not appear even with a coarse diet. Additional work on the control of pain and secretion with atropine and recognition that alkalis stimulate gastric acidity after a latent period have led to a much more liberal feeding regimen.

Smooth Diet for Peptic Ulcer.—A diet normal in respect to food constituents, with the exception of meat extractives and a few of the strong vegetables, condiments and coarse food substances, such as nuts, cocoanut and seedy foods, is used. The texture is changed by puréeing or chopping all foods or by using cooked instead of raw fruits and vegetables. The amounts given at a meal are normal or small, depending on the hunger and capacity of the patient. Milk is given at regular intervals, at 9 A.M. and 3, 7 and 9 P.M., if the pain persists.

Patients are able to adjust themselves to either of these diets more easily than to the usual milk and cream with additions, and a better nutritive state can be maintained.

If gastric retention is marked, the servings are made smaller and the day's requirements divided into five or six meals instead of three. Milk is given between meals and at bedtime if the patient has much discomfort.

The same diet is used after gastroenterostomy, and the regimen of five small meals is used after resection or gastrectomy when the capacity of the stomach is reduced.

Care in diet after gastroenterostomy for peptic ulcer is just as important as treatment before. The length of time the diet is followed is determined by the presence or absence of pain, but the patient at no time should forget the possibility of the return of his ulcer and the seriousness of this if an operation has been performed.

Peptic Ulcer With Hemorrhage.—Since Meulengracht's report on the successful use of a liberal diet for peptic ulcer with hemorrhage, his results have been duplicated by various clinics in this country. The smooth diet regimen is suggested for such cases.

SMOOTH DIET WITH MILK

The fruits and vegetables should be in a smooth form.

Diets with smooth cellulose will contain:

- Eggs, in any form except fried
- Cottage cheese or other very mild cheese
- Ground round steak free from fat, or very tender steak, chicken, fish, crisp bacon, tender roast beef
- Whole milk, evaporated milk
- Farina, cream of wheat, rice or sieved oatmeal, cornflakes, prepared rice cereals
- White bread, toasted; macaroni and spaghetti, in moderation
- Fruits, cooked and pressed through a sieve (pears, peaches, apricots, plums, applesauce); no fruits which have seeds which go through the sieve; the juice of at least one orange strained and diluted with water or 1 glass tomato or grapefruit juice daily
- Vegetables, cooked and pressed through a sieve (omit cabbage, onions, turnips, cauliflower and parsnips)
- Well baked or mashed potato
- Butter, cream
- Cream soup, strained so that it contains no coarse particles
- Plain smooth puddings (rice, tapioca, bread, custard), plain jello, ice cream (no nuts, raisins, cocoanut, dates), sponge cake, angel food cake or sugar cookies.

Do not use bran in any form.

Avoid: Fried foods, spices, vinegar, pie, pastry and all raw foods except orange juice and grapefruit juice.

Suggested Menu

Breakfast
Strained orange juice, half water
Farina, cream and sugar
Egg
Toast and butter
Milk
Coffee, if desired

Dinner
Cream soup, crackers
Broiled ground beef
Mashed potato and butter
Sieved peas
Toast, butter
Milk
Ice cream

Supper
Cottage cheese, jelly
Baked potato and butter
Toast, butter
Sieved peaches
Milk
Baked custard

9 A. M. *Lunch*
Milk or milk and cream

3 P. M. *Lunch*
Milk or milk and cream

7 P. M. *Lunch*
Milk or milk and cream

9 P. M. *Lunch*
Milk or milk and cream

Malignant Growths.—Food should be of such character that the maximum gastric comfort is assured with all nutritive requirements covered. As much attention as possible is paid to iron- and vitamin-rich foods, since anemia, polyneuritis, cheilosis, sore tongue and bleeding gums or other symptoms of vitamin deficiencies are apt to appear. A general diet is used until the patient has difficulty with bulk; then soft, smooth or small feedings are begun. Appetite and a good nutritive state must be maintained as long as possible.

Tube Feeding.—If the patient is fed through a tube or fistula, the formula used can be complete and the caloric level sufficiently high to lead to definite weight gain.

The volume of the formula is determined by the number and size of feedings given during the day. The consistency is determined by the size of the tube or the opening.

The following formulas can be followed in the average home. It is suggested that iron be added, and if the opening is large, sieved vegetables and fruits can be added to give more bulk and a more normal stool. Prune juice and lactose also help in the problem of constipation. However, the patient has usually a small bowel movement every other day and when reassured as to this is satisfied. The water intake should be watched, and when the volume of the feeding is small, additional water should be given.

TUBE FEEDING (1)

Eggs	4
Milk	1 quart
Evaporated milk	1 7-oz. can
Karo syrup	1 cup
Vitamin B complex or yeast tablets	6
Orange or tomato juice*	1 cup
Cod liver oil	1 teaspoon

Mix first five ingredients well. Cook like soft custard in a double boiler. Cool and strain through gauze or a fine strainer. Add strained tomato or orange juice and cod liver oil after the formula has cooled.

Approximate value:	Protein	70 Gm.
	Calories	2,000
	Volume	1,500 ml.

* Pure ascorbic acid can be used.

TUBE FEEDING (2)

Eggs	4
Milk	1 quart
20 per cent cream	1 pint
Karo syrup	$1\frac{1}{2}$ cups
Vitamin B concentrate or yeast tablets	6
Orange or tomato juice*	1 cup
Cod liver oil	1 teaspoon

Mix first five ingredients well. Cook like soft custard in a double boiler. Cool and strain through gauze or a fine strainer. Add strained orange or tomato juice and cod liver oil after the formula has cooled.

Approximate value:	Protein	70 Gm.
	Calories	3,000
	Volume	1,600 ml.

The protein content of both formulas can be increased by the addition of dried skim milk powder or one of the protein-rich infant food preparations.

Lower Part of Intestinal Tract.—When the food residues pass into the colon, they contain from 90 to 95 per cent water and vary in consistency from a smooth emulsion to a curdy, coarse mixture which separates on standing. The consistency as well as the color and odor is affected by the diet and to less extent by the manner in which it is taken. The mass, however, contains little nitrogen, fat, carbohydrate or calcium and will vary in reaction from *p*H 5 to *p*H 7 or 8. Some particles of food, such as small lumps of boiled potatoes, green peas and particles of orange or peach pulp, can be recognized, but these do not represent any real loss.

Absorption of water with concentration of the fecal mass takes place in the colon. The water content of the normal stool ranges from 70 to 85 per cent.

Examination and analysis of the stools of normal, constipated and diarrheal subjects show the presence of small amounts of nutritive substances. The presence of small and relatively constant amounts of fat establishes an excellent utilization of this substance. (Pancreatic disease with failure of the enzymes to reach the upper part of the tract and failure of the bile are definite pathologic states, in which fat appears in really large quantities, 12 to 23 or even 50 per cent.) Carbohydrates, unless given in such strength as to act as a hypertonic solution, also are present in small amounts. Lactose may appear in larger amounts than the other sugars, owing possibly to its somewhat insoluble character. Starch granules can often be found, but again in insignificant amounts. The demonstration of undigested meat fibers and particles of cellulose-rich foods, such as peach, corn or beans, represents little loss of actual nutriment, but is a rather severe indictment of eating habits.

The reaction of the normal stool is alkaline and that of the diarrheal stool acid, and the looser the stool, the greater the acidity. The reaction of the stool can be modified to some extent by diet. Large amounts of meat render it more alkaline, while milk and sugar make it less so.

The normal stool is formed, smooth, sausage shaped and dark brown, has no unusual odor and is passed without undue strain or an unusual amount of gas. The appearance of any but this type of stool is some indication of disease, though it may be related to (1) poor choice of food, so that water-holding bulk is absent and the residues consist mostly of debris from the tract itself; (2) poor habits of defecation, such that the mass is allowed to remain in the tract and absorption of water occurs; (3) dysfunction of the neuromuscular mechanism, so that propulsion proceeds at an uneven rate or is so rapid that absorption of water cannot take place; (4) active inflammation and ulceration of the mucosa, so that water absorption is poor and constant irritation and stimulation lead to further upset of the neuromuscular mechanism; (5) obstruction or interference with function, particularly by growths in the tract, by abnormality in adjacent organs or by disease in the upper part of the tract.

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* Pure ascorbic acid can be used.

Appetite.—When the derangement is functional, there are usually periods of anorexia or periods of abnormal consumption of food. With inflammation of the tract or with severe diarrhea, anorexia is marked by the patient's over-consciousness of activity along the tract.

Bulk in the Diet.—The importance of bulk in the diet has been overemphasized. The work of Cowgill, in particular, has established a level, has emphasized the individual character of fecal concentration and passage and has emphasized the need for a type of bulk which holds water tenaciously.

Crude Fiber in Foods

Amount of Crude Fiber per 100 Gm. of Foodstuff

Food	*Crude Fiber, Gm.*	*Food*	*Crude Fiber, Gm.*
Rice	0.1	Raisins	1.8
Cornflakes	0.2	Almonds	2.0
Potatoes	0.3	Onions	2.0
Canned tomatoes	0.5	Cantaloupe	2.1
Lettuce	0.6	Prunes	2.4
Banana	0.6	Peanuts	2.5
Peaches	0.6	Apricots, dried	2.6
Asparagus	0.8	Pears	2.7
Cauliflower	1.0	Raspberries	2.9
Celery	1.0	Plums	4.1
Raw tomatoes	1.1	Grapes	4.3
Cabbage	1.1	Navy beans	4.4
Carrots	1.1	Dried peas	4.5
Turnips	1.1	Dates	5.5
Apples	1.2	Figs	7.3
Whole wheat bread	1.2		
Strawberries	1.2	Sieved cooked rolled oats	0.15
Rolled oats	1.3	Sieved canned peaches	0.33
Squash	1.4	Sieved canned apricots	0.51
Cranberries	1.5	Sieved applesauce	0.70
Orange	1.5	Sieved cooked dried prunes	0.71
Graham crackers	1.5	Sieved canned peas	0.74
Peas, fresh	1.7	Sieved string beans	0.92
Lima beans	1.7	Sieved canned spinach	0.95

Fruit and vegetables high in hemicellulose furnish satisfactory water-holding bulk. Agar-agar can be used, and a preparation of more or less pure hemicellulose is on the market. However, the average person with constipation related to food habits and habits of living and no real abnormality along the tract responds to a simple diet containing reasonable amounts of cellulose-rich foods and to regularity in living. Constipation does not lead to the absorption of toxins from the action of bacteria on the food residues.

The following suggestions and diet are made to handle simple constipation:

SUGGESTED ROUTINE FOR SIMPLE CONSTIPATION

Estimate the previous intake of residue-rich foods.
Increase fruits and vegetables by 200 Gm. over previous intake; otherwise the diet is normal.
Eat the same type and the same amount of food at the same time each day. In other words, breakfasts should be like each other, dinners like each other, etc.
Establish a habit of defecation at the same time each day.
Water must be taken freely, at least 8 glasses daily, 2 of them before breakfast.
Take a large proportion of the residue in the second meal before defecation.
  Example: If defecation usually occurs after breakfast, the supper should contain the largest amount of fiber.
A liberal serving of concentrated carbohydrate, such as jelly, stick candy or very sweet fruit juice, added at this time helps to produce a moist stool.

HIGH RESIDUE DIET

Suggested Menu

Breakfast	*Dinner*	*Supper*
Prunes	Steak	Cheese, egg or meat
Rolled oats	Mashed potatoes, ½ cup	Baked squash, ¾ cup
Cream and sugar	Stewed tomatoes, ½ cup	Buttered peas, ⅜ cup
Poached egg	Cooked celery, ½ cup, or 2 stalks raw	Cabbage salad, ⅔ cup
Toast and butter	Head lettuce, ¼ head	Enriched bread and butter
Jam (if desired)	Enriched bread and butter	Milk
Milk	Milk	Peaches
Coffee	Ice cream	

Lunch

Orange juice (with sugar or dextrose if increased calories are needed) or fruit.

Spastic Constipation.—If there is a spastic area in the lower part of the bowel, with some pain and constipation, the bowel can still handle the water-holding bulk required for a normal stool. The patient, however, will be more comfortable if some attention is paid to the texture of the food.

Cellulose is softened by cooking, but does not lose its ability to hold water. Sieving or chopping it renders it still less irritating. The following diet, normal in everything except texture, is suggested for spastic constipation. This is one condition in which vitamin B complex concentrate produces a definite and satisfactory response greater than that produced by an increase in the vitamin-rich foods in the diet.

SMOOTH DIET

The fruits and vegetables should be in a smooth form.
The sugar should be moderate in amount.
The smooth diet will contain:
  Eggs, in any form except fried
  Cottage cheese or other very mild cheese
  Ground round steak free from fat, or very tender steak, chicken, fish, crisp bacon, tender roast beef
  Milk: At least 1 pint daily
  Farina, cream of wheat, rice, sieved oatmeal, cornflakes, prepared rice cereal
  White bread, toasted or one day old; macaroni or spaghetti, in moderation

Fruits, cooked and pressed through a coarse sieve: pears, peaches, apricots, plums, applesauce; no fruits which have seeds which go through the sieve; the juice of one orange or grapefruit (strained and diluted with water) or 1 glass tomato juice daily
Vegetables, cooked and pressed through a sieve (omit cabbage, onions, turnips, cauliflower, parsnips)
Well baked or mashed potato
Butter and cream, in moderation
Cream soup (strain out coarse particles)
Plain smooth puddings (rice, tapioca, bread), custard, plain jello, ice cream; no nuts, raisins, cocoanut, dates; sponge cake, angel food cake or sugar cookies (no frosting)
3 tablets vitamin B complex concentrate daily.

Avoid: Fried foods, spices, vinegar, pie, pastry and all raw foods except orange juice and grapefruit juice.

Do not use bran in any form.

Suggested Menu

Breakfast	*Dinner*	*Supper*
Strained orange juice, half water	Cream soup (tomato)	2 slices crisp bacon
Farina	Crackers	Baked potato and butter
Egg	Ground beef broiled or cooked in broth	Toast, butter
Toast, butter	Mashed potato and butter	Sieved beets
Milk	Sieved peas	Sieved peaches
Cream, sugar	Toast, butter	Milk
	Milk	Baked custard
	Ice cream	

Lunch if desired.

Irritable Colon.—The use of a diet rich in the vitamin B complex and normal in every respect except texture is accepted for the train of symptoms which Jordan called irritable colon. Coarse foods of any kind, bran-rich cereals, etc., are either omitted from the diet or puréed if they lend themselves to this. Fruits and vegetables with the exception of orange and grapefruit juice are cooked and sieved. Regularity in kind and time of feeding, in going to stool, in sleep, etc., must be emphasized. The smooth diet may need to be followed for many months. Change to the normal diet must be made gradually, unsieved foods and then raw foods being added if no discomfort or return of symptoms ensues. If the gastric analysis has shown a poor secretion of hydrochloric acid, addition of this substance may prove highly desirable, especially when occasional diarrhea is one of the symptoms.

Vitamin B complex concentrate has been effective in many cases in reëstablishing intestinal tonus, even though there were no signs of a clinical deficiency. Again, large quantities of vitamin B-rich foods such as cereals have not been so effective as the concentrate.

Ulcerative Colitis.—Because of failure of appetite and the patient's feeling that food is responsible for the frequent stools of ulcerative colitis, food consumption is so poor that signs of deficiency states, such as anemia and low serum protein level, with edema, sore tongue and skin changes, are marked. Besides, the patient is usually dehydrated, as fifteen or sixteen stools a day, even of small volume, represent a good deal of fluid loss. Examination of the stools for calcium, phosphorus and nitrogen shows remarkably small amounts. If the patient takes food in proportion to his actual needs, he can be held in nitrogen balance. Deficiencies, with the possible exception of vitamin B_1 deficiency, are due primarily to failure of intake rather than to loss through the stool.

The influence of the mere taking of food on the desire to defecate is not well established. Certainly the normal adult does not experience this response. With ulcerative colitis it would seem that there is unusual hyperactivity or response to the usual urge to defecate or an unusual consciousness on the part of the patient, probably both. On the other hand, any and all kinds of meals have been given such patients with no increase in the number of stools, and usually as the patient's intake of food becomes normal and his nutritive state improves, he loses much of this fear of food in relation to frequent defecation.

Some control of the texture of the food at its entrance to the colon will prevent much discomfort, but reëducation of the patient in regard to food must be attempted. Nearly always he is convinced that any food, especially fruits and vegetables, will cause diarrhea. With fifteen or sixteen stools daily, some cannot help following closely on a meal. It is also evident to the patient, if he is willing to coöperate, that ingestion of a normal amount of food does not increase either the number or to any extent the volume of the stools.

Studies on the food residues from an opening at the ileocecal level showed that boiled milk gives a smoother residue than raw; that meat in any form produces a thick smooth mixture with high alkalinity; that bread and jelly, cooked cereals, cornflakes and the various rice preparations are all satisfactory; that of the fruits and vegetables, sieved pears or canned pears, sieved applesauce, ripe bananas, puréed tomatoes, tomato juice, puréed peas, spinach, strained creamed corn and mashed potatoes can be used. All the simple puddings, ice cream and sherbet also are satisfactory. Protein, particularly liver and meat, must be used liberally as protection to the liver and as building material for serum proteins, which are usually depleted. In addition, pectin in one of the common household forms has proved of some value in producing a less watery stool in colitis. With decrease in the number and change in the character of stools, the patient shows an increase in appetite.

Change to a diet of normal texture is made as the patient has the desire and courage to try it. If it will help his appetite and food consumption, this change should be made long before the stools are normal. The patient must be guarded from infections of the upper part of the respiratory tract, which so often precipitate an acute stage of the disease. Recovery may be complete from the standpoint of ulceration, but with the colon so scarred that function will never be quite normal. Nevertheless, a patient adjusts himself to some frequency of stools if they are not accompanied with pain or bleeding. Vitamin B complex has been used in large amounts, but so far no results, such as decreases in number of stools or changes in the water content, have been obtained. As the stools decrease in number, appetite improves independently of vitamin B medication. Nicotinic acid, though valuable for many unexplained diarrheas, has not so far been reported as particularly useful for this condition.

SMOOTH DIET

(Ulcerative Colitis)

The fruits and vegetables should be cooked and sieved.

The amount of liquid between meals should be controlled.

The diet will contain:

- Eggs, in any soft form, not fried
- Cheese: Cottage cheese or other very mild cheese
- Meat: Tender beef in any form except fried, chicken, fish, crisp bacon, liver
- Milk[*]: At least 1 quart daily
- Cereal: Farina, cream of wheat, rice, sieved oatmeal, puffed rice, rice krispies, cornflakes
- White bread which is not too fresh or may be toasted; macaroni or spaghetti, in moderation; crisp white crackers or saltines; no graham crackers
- Fruits cooked and pressed through a sieve. Dried peaches, apricots, plums, applesauce; no fruits which have seeds which go through the sieve (canned pears may be used unsieved); the juice of at least one orange (strained and diluted with water) daily
- Vegetables, cooked and pressed through a sieve (omit cabbage, onions, turnips, cauliflower and parsnips)
- Potatoes: Well baked or mashed
- Butter and cream, in moderation
- Soups: Cream soup, beef stock
- Desserts: Plain smooth puddings (rice, tapioca, bread), custard, plain jello, ice cream, plain sponge cake, plain angel food cake or sugar cookies (no nuts, raisins, cocoanut, dates).

Avoid: Fried foods, spices, vinegar, pie, pastry and all raw foods except orange juice and grapefruit juice.

Do not use bran in any form.

Suggested Menu

Breakfast	*Dinner*	*Supper*
Strained orange juice, half water	Cream soup, crackers	Creamed chopped beef or fish
Farina, cream and sugar	Scraped beef	Baked potato and butter
Egg, crisp bacon	Mashed potato and butter	Toast and butter
Coffee (if desired) or boiled milk or cocoa	Sieved peas	Sieved peaches
Toast and butter	Toast and butter	Boiled milk or cocoa
	Boiled milk or cocoa	Baked custard
	Ice cream	
10 A. M. *Lunch*	3 P. M. *Lunch*	9 P. M. *Lunch*
Boiled milk or cocoa	Tomato juice	Hot milk, ground chicken, or cheese sandwich

$\frac{1}{2}$ to $1\frac{1}{2}$ cups of household pectin is given daily in three portions. It is diluted with water or fruit juice as the patient desires.

Colostomy.—After colostomy, dietary care has three aims: (1) the formation of a smooth type of residue at its entrance to the colon; (2) concentration of the residue to as great an extent as possible so that care of the opening will be simple and collection will be on a pad instead of in a colostomy cup and (3) maintenance of a good nutritive state.

Studies on fistulas at various levels showed that the nearer the opening is to the small intestine, the greater the difficulty of concentration; that important food nutrients are practically absorbed by the time the residue reaches the ileocecal valve, and that foods influence the type of residue appearing at the opening.

The following dietary regimens have been worked out:

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[*] Milk should be boiled before using; buttermilk can be used if desired.

DIET FOR COLOSTOMY PATIENTS

ROUTINE I

The fruits and vegetables should be cooked and sieved.

The amount of liquid with meals should be controlled.

The diet will contain:

- Eggs, in any soft form, not fried
- Cheese: Cottage cheese or other very mild cheese
- Meat: Tender beef in any form except fried; chicken, fish, crisp bacon
- Milk*: at least 1 pint daily
- Cereal: Farina, cream of wheat, rice, sieved oatmeal, puffed rice, rice krispies, cornflakes
- White bread which is not too fresh or may be toasted; macaroni or spaghetti in moderation; crisp white crackers or saltines; no graham crackers
- Fruits cooked and pressed through a sieve: dried peaches only, apricots, plums, applesauce; no fruits which have seeds which go through the sieve (canned pears may be used unsieved); the juice of at least one orange (strained and diluted with water) daily
- Vegetables, cooked and pressed through a sieve (omit cabbage, onions, turnips, cauliflower and parsnips)
- Potatoes: Well baked or mashed
- Butter and cream, in moderation
- Soups: Cream soup, beef stock
- Desserts: Plain smooth puddings (rice, tapioca, bread), custard, plain jello, ice cream, plain sponge cake, plain angel food cake or sugar cookies; no nuts, raisins, cocoanut, dates.

Avoid: Fried foods, spices, vinegar, pie, pastry and all raw foods except orange juice and grapefruit juice.

Do not use bran in any form.

Suggested Menu

Breakfast	*Dinner*	*Supper*
Strained orange juice, half water	Cream soup, crackers	Crisp bacon
Farina	Scraped beef	Baked potato and butter
Egg	Mashed potato and butter	Toast and butter
Coffee (if desired) or boiled milk or cocoa	Sieved peas	Sieved peaches
Toast and butter	Toast and butter	Boiled milk or cocoa
	Boiled milk or cocoa	Baked custard
	Ice cream	

10 A. M *Lunch*	3 P. M. *Lunch*
Boiled milk or cocoa	Boiled milk or cocoa

ROUTINE II

The fruits and vegetables should be cooked.

The amount of water with meals should be controlled.

The diet will contain:

- Eggs, in any soft form or hard cooked in shell at least thirty minutes, not fried
- Cheese: Cottage cheese or other very mild cheese
- Meat: Lamb, roast beef, steak, chicken, fish, crisp bacon, boiled beef, baked liver
- Milk†: At least 1 pint daily
- Butter and cream, in moderation
- Cereal: Farina, cream of wheat, rice, oatmeal, cornflakes or prepared rice cereals
- White bread which is not too fresh or may be toasted; macaroni, noodles and spaghetti, in moderation; crisp white crackers or saltines; no graham crackers
- Fruits: Cooked pears, apricots, plums, applesauce, prunes, dried peaches, dried apricots, peaches; no fruits which have seeds; the juice of at least one orange daily; very ripe pear or banana, orange or grapefruit sections raw

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* Milk should be boiled before using. Buttermilk can be used if desired.

† Milk should be boiled and cooled for drinking or used in cocoa, soup, puddings, etc. Buttermilk may be used if desired.

Vegetables: Cooked string beans, peas, carrots, spinach, asparagus, beets, tomatoes, squash; no raw vegetable except lettuce (avoid cabbage, onions, turnips, cauliflower, parsnips)
Potatoes: Well cooked in any simple form
Soups: Cream soups and meat broth
Desserts: Plain puddings (rice, tapioca, bread), custard, jello, ice cream, plain sponge cake, plain angel food cake, sugar cookies; no nuts, raisins, cocoanut, dates.

Avoid: Fried foods, spices, vinegar, pie, pastry, all raw foods except oranges, orange juice, lettuce, very ripe pears, ripe bananas, grapefruit.

Do not use bran in any form.

Suggested Menu

Breakfast	*Dinner*	*Supper*
Orange juice or fruit	Soup, crackers	Cottage cheese
Farina	Roast beef	Baked potato and butter
Egg	Mashed potato and butter	Bread and butter
Toast and butter	Buttered peas	Lettuce and banana salad
Boiled milk or cocoa or coffee, if desired	Bread and butter	Boiled milk or cocoa
	Ice cream	Jello with custard sauce or cream

10 A. M. *Lunch*	3 P. M. *Lunch*
Boiled milk or cocoa	Boiled milk or cocoa

ROUTINE III

When the bowel movements are well controlled, a greater variety of foods may be added: raw fruits and vegetables and well cooked ham. If no difficulty is experienced, these may become a part of the regular diet.

Also milk which has not been boiled may be tried.

At all times it will probably be advisable to use care with the following foodstuffs: Cabbage, turnips, onions, corn on the cob or whole kernel corn, nuts (unless ground), raisins, cocoanut, berries with large seeds, highly spiced or seasoned foods, such as chili, and large amounts of candy or sweets at one time.

Regular food habits as to time of eating and amounts should be observed.

Enough should be eaten at all times to maintain a good weight and strength.

Gastric upsets from over-eating or eating poorly prepared or rich foods should be avoided.

Biliary Tract.—In diseases of the biliary tract, dietary care should cover a number of points: 1. Texture, consistency and amount of food should be planned to make the minimum demands on the whole gastrointestinal tract. 2. Some control of the emptying of the gallbladder itself should be attempted, so that a free flow of bile can be assured except when obstruction is present. 3. The secretion of bile by the liver should be stimulated. 4. All possible protection should be afforded the liver.

Efforts at making the patient with biliary disease more comfortable are along the line of prevention of any acute attack, either directly, owing to food, or indirectly, by disturbance elsewhere in the gastrointestinal tract.

Control of Weight.—One of the primary points is the control of weight. If the patient is over-weight, not only can reduction be a part of the scheme but the fact that the lessened amounts and the difference in the kinds of food lead to fewer gastrointestinal upsets must be emphasized.

The reduction diet in the presence of biliary disease may need to be smooth—or at least much of the fruit and vegetables should be cooked rather than raw—and will differ from the usual reduction diet by the omission of the strong vegetables. The diet is low in fat and has an extra allowance of protein because of its effect on the formation of bile and because of its protective values. Also, if an operation is necessary, there will be less danger of lowered serum protein. The following regimen illustrates the principles of diet to be observed:

SMOOTH* DIET—LOW CALORIE

(Approximately 1,000 calories)

Fruits and vegetables should be in a smooth form (cooked and pressed through a coarse sieve).

Breakfast

1. One of the following:
    - $\frac{1}{2}$ cup orange juice (unsweetened) and $\frac{1}{2}$ cup water
    - $\frac{1}{2}$ cup grapefruit juice (unsweetened)
    - $\frac{1}{2}$ cup pineapple juice (unsweetened)
    - 1 cup tomato juice
    - $\frac{1}{2}$ very ripe banana

    Fruit canned or cooked without sugar and pressed through a sieve:
    - $\frac{1}{2}$ cup pears
    - $\frac{1}{2}$ cup peaches
    - $\frac{1}{2}$ cup applesauce
    - $\frac{1}{2}$ cup apricots
    - $\frac{1}{2}$ cup plums
    - $\frac{1}{3}$ cup sieved, stewed, dried fruit such as: peaches, apricots, prunes (without sugar)
2. One of the following:
    - $\frac{1}{2}$ cup rice krispies
    - $\frac{1}{2}$ cup cornflakes
    - 1 cup puffed rice
    - $\frac{1}{2}$ cup farina
    - $\frac{1}{2}$ cup sieved oatmeal

    or

    1 small slice toasted white bread
3. 1 teaspoon butter
4. Two to four slices very crisp bacon
5. 1 cup skim milk
6. Coffee, if desired
7. Saccharin, if desired
8. 1 teaspoon cod liver oil

Dinner and Supper

1. One of the following:
    Serving—4″ x $2\frac{1}{2}$″ x $\frac{1}{2}$″, $3\frac{1}{3}$ ounces or 100 Gm. of scraped beef, cubed round steak, roast beef, lean steak, fish, chicken *or* $\frac{1}{2}$ cup creamed dried beef made with skim milk *or* $\frac{1}{2}$ cup cottage cheese
2. 1 cup of one of the following:
    - (vegetables cooked and sieved)
        - string beans
        - tomatoes
        - spinach
        - beet greens
        - asparagus
        - celery
    - (fruits canned without sugar and sieved)
        - peaches
        - pears
3. $\frac{1}{2}$ cup of one of the following:
    - (vegetables cooked and sieved)
        - beets
        - peas
        - squash
        - carrots
        - pumpkin
    - (fruits canned without sugar and sieved)
        - apricots
        - applesauce
        - pears
        - blue plums
4. 1 cup skim milk or buttermilk
5. Saccharin, if desired
6. 1 vitamin B complex tablet

This has a value of 1,000 calories and will bring about a satisfactory reduction in the woman of average size. If the patient is a woman 5 feet tall or under, 200 calories should be dropped out; for the taller woman (5 feet 5 inches or more) or for a man, 200 calories can be added. Rapidity of reduction has no untoward effects, especially for the very obese, and is psychologically stimulating to the patient.

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* Control of texture to this extent may not be necessary. The same diet can be used with the fruits and vegetables raw or cooked as in the normal diet.

If there is no question of over-weight, the normal diet with changes in texture when necessary and omission of so-called strong vegetables is used, with a period of high carbohydrate feeding before and after operative procedures. The following smooth, low fat diet is satisfactory:

GENERAL* OR SMOOTH LOW FAT DIET

The fruits and vegetables should be in a smooth form.

The smooth diet will contain:

- Cottage cheese, uncreamed
- Ground beef, tender steak, cubed round steak, roast beef, lean fish, chicken—without fat.
- Skim milk or buttermilk, at least 1 quart daily
- Farina, cream of wheat, rice, sieved oatmeal, cornflakes or prepared rice cereals
- White bread one day old or toasted; macaroni or spaghetti, in moderation
- Fruits, cooked and pressed through a sieve: pears, peaches, prunes, apricots, plums, applesauce; orange and grapefruit juice, tomato juice (do not use fruits with seeds which go through a sieve)
- Vegetables, cooked and pressed through a sieve (omit cabbage, onions, turnips, cauliflower and parsnips)
- Well baked or mashed potato
- Desserts: Plain smooth puddings (creamy rice, fruit tapioca, custard made with egg white and skim milk), sherbet, plain jello, angel food cake, meringue cookies (no nuts, raisins, cocoanut, dates or whipped cream)
- Sugar
- Jelly or honey, no jam
- Coffee or tea, in moderation, no cream.

Do not use bran in any form!

Avoid: Fried foods, spices, vinegar, pie, pastry; all raw foods except orange and grapefruit juice; fats and fatty foods, as cream, butter, mayonnaise, etc.; egg yolks.

Suggested Menu

Breakfast	*Dinner*	*Supper*
Orange juice, half water	Roast beef	Cottage cheese or broiled meat cake
Farina	Mashed potato or rice	Sieved tomatoes
Creamed dried beef (use skim milk for white sauce)	Sieved peas	Baked potato and $\frac{1}{2}$ square butter
Toast, jelly	Toast, jelly	Toast, jelly
Skim milk	Skim milk	Sieved peaches, angel food cake
Coffee, if desired	Sherbet	Skim milk

The importance of a normal gastric mechanism to the normal functioning of the biliary system must not be overlooked. Hydrochloric acid is a factor in stimulating the formation of secretin and of bile by the liver. Gastric analysis, as well as the usual tests for gallbladder function, aids in planning dietary and other care. Normal bowel action must be promoted also, and the foregoing diets with the normal amount of fiber, though changed in character, should control this if the patient follows proper habits.

Stimulation to Contraction of the Gallbladder.—When free emptying of the gallbladder is desired, ingestion of fats can be an aid. Olive oil is commonly used, though cream and egg yolks are good. This stimulation is most marked, however, if the fat is taken after fasting and not repeated at too frequent intervals. The use then of a fairly low fat diet with a definite dose of olive oil (2 ounces) or cream given in the morning seems logical.

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* Fruits and vegetables cooked or raw and unsieved can be used if a general diet is desired.

Cholesterol.—Control of dietary cholesterol as a means of affecting the concentration of this substance in the bile accomplishes little, since cholestrol is of both endogenous and exogenous origin. Blood cholesterol increases for a short time after a meal high in cholesterol and total blood fats decrease after a long period of low fat intake. Bile with normal constituents and in normal amounts appears from five to seven days after bile drainage regardless of the diet. The appearance of normal bile from the drainage tube is always delayed when considerable liver damage was observed at the time of operation.

The normal diet contains probably 1 to 2 Gm. of cholesterol, depending on the type of meat and the number of eggs used. Diets containing less than 1 Gm. of cholesterol are complete in all the dietary essentials, though somewhat monotonous from the standpoint of types of proteins.

The cholesterol-rich foods are eggs, especially the yolk, glandular meats and fats, including butter and cream. Less rich are lean beef, chicken, veal, fish, cereals and milk. Fruits and vegetables contain plant sterols, but their relation to cholesterol formation in the body is undetermined.

The Liver.—The liver is stimulated to bile formation by meat, given either alone or in a mixed diet. This stimulation is especially noticeable when the meat is given after fasting. The diet (general or smooth, with low fat content) given previously contains meat twice daily. One pint of milk can be omitted and a third serving of meat added if this method of bile formation is desired.

Protection to Liver.—The liver can be protected against fatty infiltration, damage by lipid and fat solvents such as anesthetics and other types of damage by a diet high in carbohydrate and proteins. Regeneration of liver cells and of serum proteins follows high protein feeding.

Carbohydrate fortification before operative procedures has proved valuable. One pint of fruit ade sweetened with dextrose at 10 A.M., 3 P.M. and 9 P.M. and eight to ten sticks of candy during the day may be given. A stick candy which is neither so hard as to irritate the mouth nor so soft as to prove cloying should be chosen. If the patient is over-weight, this supplement is added to the reducing diet three days before operation.

A liquid diet high in carbohydrate should be used when the patient begins to take food again, and the smooth high protein diet may be necessary for some time after operation. Bile and bile salts are stimulants to the biliary tract, and the return of bile in drainage cases either by stomach tube or in a cocktail not only promotes bile formation and contraction of the gallbladder but aids materially in reëstablishing normal digestive processes along the tract itself.

Bile or bile salts is necessary also to the vitamin K cycle and the formation of prothrombin. Neither is effective, however, if liver damage is extensive.

Alfalfa seems to be a good source of vitamin K and has been the source of a great many of the vitamin K concentrates used in experimental work. Vitamin K is present in liver, spinach, kale and other green leafy vegetables and is elaborated by many microörganisms. It is doubtless widespread or the human requirement is exceedingly small, since the deficiency in the human being is recognized only in connection with lack of bile in the intestinal tract or with certain types of extensive liver damage.

A careful check on the serum proteins before and after operation will indicate the need of protein additions in order to prevent too great a decrease with attendant edema.

High Protein Diet.—Many patients come to the hospital with a long history of dietary restrictions, and after anesthetic and operative procedures, profound decreases in serum protein are seen.

As shown by Whipple, milk, liver and beef proteins are the most efficient in bringing about regeneration. The higher the protein level, the more difficult it is to administer the diet, to make it attractive and palatable and to have it within normal limits of intake. Fluid and salt restrictions are of minor importance, and failure of regeneration with continued edema is usually due to the patient's inability or unwillingness to take the extra and necessary proteins, unless, of course, the liver is badly damaged.

The following diet gives the distribution and form of protein at the 120 Gm. level. No restrictions are made as to kind, and the texture and consistency of the diet are determined by the patient's ability to take solid food. Additions of small amounts of salt to make the food palatable will lead to only a transitory increase in the edema at best, if the patient actually consumes the protein. Restrictions in fluid should be made to affect the water intake as such and not the total liquids, since milk is not only an efficient protein but can and should be made the carrier of other proteins, such as egg or dried milk powder or the high protein preparations used in infant feeding, valuable forms of additional protein. The following formula illustrates this:

HIGH PROTEIN DIET

(Approximately 100 to 120 Gm.)

Breakfast

1. Fruit with sugar
2. 2 eggs, ham
3. Milk, 1 glass
4. Toast and jelly
5. Cereal, milk and sugar

Dinner and Supper

1. Fruit juice with dextrose
2. 2 eggs *or* 1 serving of cheese *or* 1 large serving of meat, fish, or chicken
3. Green vegetables (omit cabbage, onions, turnips, cauliflower, navy beans)
4. Potato, sweet or white
5. Fruit as sauce or salad
6. Milk
7. Desserts made with egg and served with caramel or sweetened fruit sauce or New York ice cream with sauce
8. Sugar, jelly, honey and butter, as desired

10 A. M.

Eggnog or chocolate milk

3 P. M.

Fruit juice and meat or egg sandwich

7 P. M.

Hot chocolate milk

Avoid: All highly seasoned foods, vinegar, tea, coffee.

CHOCOLATE MILK

	Protein, Gm.
1,000 Gm. or 1 quart milk	33
50 Gm. casec	44
30 Gm. chocolate syrup	1
Yield—5 servings	78

A small serving of ice cream is added to each glass usually.

Protein at levels of 2 Gm. or more per kilogram of body weight should be used, but patients needing this type of diet are seldom able or willing to eat so much protein and enough carbohydrate for their energy needs. This had led to the use of aminoacid mixtures orally or intravenously. Reports vary somewhat as to results from this type of feeding but on the whole seem favorable.

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PART VI

Gastrointestinal Manifestations of Extra-abdominal and Systemic Diseases

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CHAPTER XXXVIII

THE RELATION BETWEEN THE GASTROINTESTINAL AND CARDIOVASCULAR SYSTEMS

Introduction.—From time immemorial, disorders of the "stomach" and of the heart have been a source of great confusion, and not even yet has the problem been completely solved (White). The question is not simply which organ is responsible in any given case; often the degree of responsibility of each for symptoms and signs in the real problem.

Anatomically and reflexly the heart and the stomach are near neighbors. Even during perfect health they react on each other profoundly. A full stomach raises the diaphragm and with it the heart and elevates the metabolism and the heart rate; exercise and hot baths dilate the peripheral circulation and slow the digestive processes; good muscle tone and a healthy circulation favor normal bowel function, and fear may depress both systems. These simple effects in health must be taken into account as additional factors in the presence of diseased heart or stomach. Thus, a stomach distended by a hearty meal may have no harmful effect on the circulation of a normal person but can readily induce coronary insufficiency with angina pectoris or myocardial failure with acute pulmonary edema when coronary or myocardial reserve is low; and paroxysmal tachycardia, a simple disorder of cardiac function, may induce cardiospasm through a reflex mechanism more easily if the stomach is already irritable, as from gastritis, ulceration or a hiatus hernia.

An odd but unimportant variation from normal is congenital situs inversus, with the heart, stomach and spleen on the right side and the liver on the left. This is frequently overlooked until *x*-ray studies are made of the thorax or abdomen. There are no symptoms associated with this anomaly. The discovery of the dextrocardia may furnish the clue to the altered positions of the abdominal viscera.

Effect of Gastrointestinal Diseases on the Heart and Circulation.—Gastrointestinal, gallbladder and liver diseases *per se* do not cause structural changes in the circulation—that is, disease of heart and bloodvessels—notwithstanding the occasional teaching that gallstones are responsible for coronary heart disease with angina pectoris, for example. There are three reasons for former misconceptions: (1) gastrointestinal disorders may simulate heart disease; (2) they may initiate disorders of cardiovascular function, harmless when the heart is normal but sometimes serious when myocardial or coronary reserve is very low; (3) they may coincide with cardiovascular disease, either independently or through a common factor.

These statements apply particularly to *gallbladder disease with stones,* which may simulate coronary thrombosis with myocardial infarction, may reflexly produce extrasystoles or paroxysmal tachycardia or even paroxysmal auricular fibrillation, may cause the myocardium to fail or aggravate angina pectoris and is more often found in persons with than in those without high degrees of coronary arteriosclerosis, apparently owing to a common aging factor (Walsh and associates). But there is no indication that the gallbladder disease itself actually causes the heart or coronary artery disease. Finally, gallstones may produce a profound temporary effect on the general circulation; colic may lead to syncope or even, rarely, in old persons to collapse and vascular shock. The correction of gallbladder disease by diet or operation may clear up the symptoms of cardiovascular trouble, but in the presence of serious heart disease, serious surgical operations such as cholecystectomy should be avoided except when necessary.

A second important gastrointestinal disease which has sometimes been related to heart disease in medical writings is *ulcer of stomach or duodenum.* However, this is much less likely than gallstones to be associated with heart disease; their concurrence is largely coincidental (Walsh and associates). It is true, however, that such ulceration may, like gallstones, though less often, act reflexly to stir up cardiac arrhythmia. Severe bleeding may cause an anemia great enough to produce cardiac dilatation with murmurs correctible by transfusion or other treatment of the anemia; and of course severe hemorrhage may induce profound shock and in rare cases of heart disease even myocardial or coronary failure.

Much more irritating to the heart than ulcer is *cardiospasm* or *esophageal spasm* with or without actual gastritis or a *hiatus hernia.* A full stomach, aerophagia or excessive use of tobacco may initiate a spastic state which in turn may apparently result in angina pectoris in a person with coronary heart disease or in cardiac arrhythmia whether there is heart disease or not.

Similarly, *irritability, distention* or *inflammation of the colon* may set off cardiac symptoms when the heart is irritable or diseased or even arrhythmia (extrasystoles, paroxysmal tachycardia or paroxysmal auricular fibrillation) when the heart is normal. These things, however, do not cause heart disease as such, but it is of the greatest importance to maintain the good health of the entire gastrointestinal tract of a cardiac patient with limited myocardial or coronary reserve.

Diseases of the liver and pancreas do not cause lesions of the heart or bloodvessels, but if serious they do depress the function of these structures, whether healthy or diseased.

Effect of Cardiovascular Diseases on the Gastrointestinal Tract.—Heart disease has apparently a much greater influence on the stomach, bowels and liver than has gastrointestinal disease on the heart, but this effect is limited to a few conditions only. The great majority of cardiac patients have a normal gastrointestinal tract or only incidental trouble therein. I shall now discuss in the order of importance the cardiac conditions that influence the structures below the diaphragm.

Congestive failure of the right ventricle has a direct and serious effect on the liver, which, like the lung in left ventricular failure, can soak up a lot of blood when the systemic venous pressure is unduly elevated. The hepatic and portal circulations, with their low effective pressures and with the hepatic veins entering the inferior vena cava at such an angle that they are apparently easily compressed, bear the brunt of the congestion early. The liver swells quickly and may vary rapidly in size up or down, depending on variations of the systemic venous pressure. It shows the effect of the heightened pressure even sooner and more than do the jugular veins. *Pain* in the right hypochondrium is a common symptom of the early stages of swelling of the liver with right ventricular failure, especially if the disease is acute and of high degree. In fact, it may appear only on effort at first, like dyspnea on effort due to acute congestion of the lungs in the early stages of left ventricular failure (Boyer and White).

The liver may become enormous in heart failure, reaching even to the umbilicus or below, but it has the striking capacity of shrinking rapidly as the congestion subsides; even in forty-eight hours, under treatment by rest or digitalis or diuretic medication, alone or in combination, the edge of the liver can recede from the umbilicus to the costal border.

Two other cardiac conditions besides failure of the right ventricle can make the liver swell: tricuspid valve disease, with stenosis or regurgitation or generally both, and acute or chronic constrictive pericarditis. With *tricuspid valve disease,* there is a chronic deep systolic pulsation of the jugular veins and of the liver, with a full venous pulse pressure and possibly actual myocardial failure or raised venous pressure in diastole; in fact, the greater the myocardial (congestive) failure, the less the venous pulsation but the greater the venous engorgement. With marked disease of the tricuspid valve, the liver remains enlarged for years, much longer than with myocardial failure, but for a period comparable with that for constrictive pericarditis. In fact, tricuspid stenosis protects the heart from the burden of over-work by restricting the amount of blood entering it, and the patients with rheumatic heart disease who live the longest after congestion of the liver and peripheral edema appear are those with tricuspid stenosis complicating their mitral stenosis (Levine and Thompson). On the other hand, this is no real advantage, for patients with tricuspid involvement are hit hardest by the rheumatic infection and die earlier than those who do not have such prolonged congestion (Cooke and White).

Another potent though not common cause of swelling of the liver, acute or chronic, is *pericardial constriction,* either acute with effusion (cardiac tamponade) or chronic when due to the contraction of thick pericardial scar from fulminating extensive but not fatal infection. In both acute and chronic constrictive pericarditis the venous pressure is much raised and the arterial output reduced. These findings, along with an abnormal electrocardiogram (depressed or inverted T waves) in the face of an otherwise normal heart (little if at all enlarged), help to distinguish the enlarged liver of constrictive pericarditis from intrinsic liver disease (with cirrhosis).

Cardiac cirrhosis of the liver is a definite entity, but it is rarely extreme. Slight involvement is not uncommon in the presence of prolonged chronic extensive congestion resulting from any of the three cardiac conditions already mentioned. Often, however, histologic examination, even after years, has revealed little but chronic vascular engorgement of the liver.

Finally, raised systemic venous pressure from any of the causes aforementioned, but by far most commonly from heart muscle failure, results in *engorgement and disturbed function of the other contents of the abdomen:* stomach, small and large intestines and rectum, pancreas and spleen. Digestion is disordered; meteorism is common; constipation occurs, and anorexia is the rule. Much care must be devoted to preventing *malnutrition and avitaminosis,* which are secondary in advanced disease and due in turn to gastrointestinal complications in the treatment of heart failure.

Coronary insufficiency is another important disorder of the circulation that may have some gastrointestinal repercussion, although the effect is transient and not serious. Not uncommonly patients with angina pectoris have esophageal spasm or cardiospasm, often with the belching of gas, at the time of their acute coronary insufficiency; this is apparently induced reflexly. Nitroglycerin relieves both cardiac and gastric pain, the former more rapidly than the latter.

Acute myocardial infarction from coronary thrombosis rarely excites gastrointestinal symptoms. Nausea and vomiting, when they occur, are due more often to the narcotic given for relief of the pain than directly to the disease. Similarly, the distention and constipation that frequently complicate the convalescence following myocardial infraction are doubtless due to the absolute rest imposed and the limited diet, with or without the added effect of sedatives. However, one result of myocardial infarction may seriously involve the gastrointestinal tract: Intracardiac thrombosis may be the source of an embolus to the mesentery, fortunately a rare complication.

Embolism involving the gastrointestinal tract is in its totality not rare, although any one cause is decidedly uncommon. Among its causes, besides myocardial infarction (just mentioned), are mitral stenosis or cardiac arrhythmia, or both, with auricular stasis and thrombosis; subacute (or acute) bacterial endocarditis, thrombosis of an aortic aneurysm; thrombosis over a plaque of an atheromatous aorta, and thrombosis in the pulmonary veins.

Arrhythmias of the heart only rarely affect the gastrointestinal tract. However, they may reflexly (as in angina pectoris) induce cardiospasm. Still less often they cause congestion by inducing heart failure. Finally, they may produce an embolism to block a mesenteric artery from a mural thrombus.

Aneurysms of the aorta not infrequently compress, block and erode the esophagus, and a dramatic cause of death in such cases is the outpouring of blood from rupture of a syphilitic aneurysm into the esophagus or stomach. Dissecting aneurysms of the aorta may block the blood supply to the gastrointestinal tract by pressure on the mouths of the arterial branches.

Enormous enlargement of the left auricle, sometimes called "aneurysm of the auricle," in disease of the mitral valve displaces the esophagus backward and usually to the right, although rarely a left displacement is noted by *x*-ray. Symptoms from such displacement in such cases are rare indeed.

Congenital defects of the aorta and its branches may also compress and displace the esophagus (and trachea), with resultant dysphagia and even erosion. In particular, a right aortic arch, a double aortic arch and a right subclavian artery arising from the descending thoracic aorta are responsible for such disorders.

Finally, notice should be taken of a rare but important condition, *splenic vein thrombosis,* probably the cause of Banti's disease, which results in *esophageal varices,* a potent source of serious and even fatal hemorrhage.

Differential Diagnosis.—The greatest problem so far as the relation of gastrointestinal and cardiovascular systems is concerned is the confusion of diagnosis, dependent primarily on pain. All other symptoms, such as dyspnea and nausea, are helpful though by no means reliable clues.

Pain due to coronary insufficiency (angina pectoris) can exactly duplicate in almost all its features that due to esophageal spasm (or cardiospasm), no matter what the exciting cause of either. Position (substernal), character (oppressive or even burning, not sharp), duration (a few minutes) and even response to nitroglycerin may be the same. However, there are usually some differences in character, the pain of cardiospasm fitting more often the designation "heartburn," and angina pectoris yielding more quickly to nitroglycerin. There is one point of major difference, the circumstances. Angina pectoris occurs primarily and maximally on effort; rarely does it follow rest or eating until the coronary insufficiency is far advanced and has already followed effort for weeks or months. The discomfort of cardiospasm is primarily or maximally set off by eating, especially a hearty meal, by excitement or by smoking. It is true that angina pectoris on effort is much more likely after than before meals, but even in the presence of both angina pectoris due to coronary insufficiency and the discomfort caused by cardiospasm, a distinction between the two is possible if the subject is observant and has had "indigestion" for some years before he acquires the angina pectoris. However, the close similarity of the pains and the fact that one may excite the other have even raised the conjecture that angina pectoris itself is really but an esophageal spastic manifestation of the heart disease (Jackson and Jackson). The chief arguments against such a theory are the prolonged severe pain in acute myocardial infarction when heart muscle is dying and the fact that no relief follows the use of nitrites and atropine to abolish all possible spasticity of stomach and esophagus. Such pain in coronary thrombosis exactly duplicates that of angina pectoris except for duration (hours rather than two or three minutes).

Belching of gas is characteristic though not universal with cardiospasm; it usually does not accompany angina pectoris, although it may occur if cardiospasm is induced secondarily.

One other gastrointestinal cause of pain that may stimulate important cardiovascular pain is *biliary colic*. Sometimes this may occur in the epigastrium or under the lower end of the sternum and last for hours; it can be mistaken, unless one is very careful, for *acute myocardial infarction* secondary to coronary thrombosis. With biliary colic, the pain more often radiates to the back; there is greater likelihood of nausea and vomiting, with an old history of indigestion, and the electrocardiogram fails to show evidence of acute heart muscle damage. However, a history of both conditions (not simultaneous) is not rare, particularly when the patient is getting on in years.

Perforation of a gastric or duodenal ulcer and *mesenteric embolism or thrombosis* rarely simulate coronary thrombosis or dissection of the aortic wall; localized abdominal tenderness and spasm, cardiac abnormalities (present only coincidentally) and electrocardiographic evidence help in the differentiation.

Practically no other sources of pain in the gastrointestinal and cardiovascular tracts are of importance, either *per se* or in differential diagnosis. The heartache of neurocirculatory asthenia, the pain of pleuropericarditis, hyperacidity pain and pylorospasm and the pain of appendicitis and of distention of the colon are all too characteristic for attention here.

Tenderness on palpation is common with gastrointestinal disease, often localizing the trouble. With cardiovascular disease it is notably rare except over an acutely congested liver or as a nervous manifestation; in fact, precordial tenderness is actually a favorable point in prognosis, being much more common with cardiac neurosis or neurocirculatory asthenia alone than with serious heart disease.

Anorexia, nausea and vomiting strongly favor the diagnosis of gastrointestinal disease except in three situations, when they may be found accompanying heart disease: (1) as a reaction to overdosage of digitalis in the treatment of congestive heart failure or of the tachycardia of auricular fibrillation or flutter; (2) as a reaction to opiates given to relieve the pain of myocardial infarction or the dyspnea of acute pulmonary edema and (3) in the presence of congestion of the stomach and liver in heart failure. The first two are more common associations than the last. However, it is important to remember that gastrointestinal disease accompanying heart disease may be the answer.

Jaundice strongly favors the diagnosis of gallbladder or liver disease, but it may rarely accompany congestive heart failure with an engorged, malfunctioning liver when pulmonary infarction complicates the picture. Then the excess of blood pigment derived from the resolution of the infarct cannot be adequately handled by the liver, a serious but not necessarily fatal omen.

Hiccoughing strongly favors gastrointestinal or gallbladder disease; it is rare with heart trouble.

Dyspnea, past or present, of course favors heart disease, though pulmonary emphysema may cause it to accompany gastrointestinal trouble.

Palpitation is even less diagnostic; it is commonly found when the heart is normal as a manifestation of trouble below the diaphragm.

Laboratory data are occasionally decisive in differential diagnosis; for example, a positive Graham test in a case of acute gallbladder disease* or electrocardiographic evidence of acute myocardial infarction. Recourse should always be had to all available methods of study when diagnosis is doubtful, but it is important to remember that silent gallstones can complicate acute myocardial infarction, and that chronic coronary or other heart disease can complicate biliary colic.

The Question of Surgical Intervention.—The commonest questions asked of the cardiac consultant by the surgeon about to undertake the operative correction of some gastrointestinal lesion are: "Can this patient stand the strain of operation?" and "How extensive a job can we do if the need arises?" There are three important considerations here to be taken into account.

First, it is important to *confirm* the diagnosis both of the heart disease and of the abdominal condition and to gage the severity of each; acute coronary occlusion superimposed on angina pectoris may simulate a subdiaphragmatic "surgical emergency," or *vice versa.*

Second, "operations of choice" should not be undertaken in the presence of even slight myocardial or coronary insufficiency because of the real hazard of serious reactions to the strain of anesthesia and operation, consisting of acute pulmonary edema, acute coronary occlusion and fatal angina pectoris.

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* One should hesitate to resort to a Graham-Cole test when an acute cholecystitic manifestation is suspected. A so-called "flat plate" may be helpful and obviate any of the untoward reactions which have been reported when the dye test is used to diagnose acute gallbladder disease.—EDITOR.

Even recurrent pulmonary embolism is much more common with cardiac disease, especially with peripheral circulatory stasis. Sometimes it is thought that the correction of trouble below the diaphragm (or as a matter of fact anywhere else) may have a favorable influence on the heart and help to build up either coronary or myocardial reserve; undoubtedly there is truth in this idea, but the difficulty lies in the danger to life from the operation itself, which is too great unless the operation is necessary. It is just such circumstances that have given rise to the familiar expression "The operation was successful but the patient died." However, in emergencies the risk must be taken. As a matter of fact, the great majority of patients with valvular disease, hypertension or old myocardial scars have neither myocardial nor coronary insufficiency and so are good enough risks for operation. Arrhythmias are not a bar to operation, except perhaps high grade heart block with Adams-Stokes attacks.

Third, if it is decided to operate on a patient with more than trivial heart disease, *detailed preoperative and postoperative care* must be planned and executed. If it is possible to postpone operation for a few days or a week or two in order to build up myocardial or coronary reserve, or at least to clear away the grosser evidences of heart failure, the risk of operation may be cut in half. If there is a choice between radical and conservative procedures, the latter should be selected. It may be possible at some later date under better circumstances to finish the job, or in the long run the conservative measure may suffice.*

The question of the administration of drugs in preparation for operation should next be considered. *Digitalis* medication is probably the most debatable. In the presence of congestive heart failure or of auricular fibrillation or flutter there is no question of its importance and value. Digitalization should be effected slowly, in the course of a week if there is time (1 to 1½ grains of the standardized powdered leaf three times a day for four to seven days); or rapidly, in the course of twelve to twenty-four hours if the need of operation is urgent or the congestive failure is marked or acute (a convenient preparation for intravenous use under such circumstances is lanatoside C, or cedilanid, 2 cubic centimeters or 0.4 mg. every four hours for three or four doses, to be followed by 1 or 1½ grains of powdered leaf by mouth daily). Debate focuses on the prophylactic use of digitalis in the absence of heart failure or arrhythmia. It certainly is not necessary for a young or middle-aged person with no heart disease, but old age or cardiac strain and enlargement at any age may justifiably warrant the use of a relatively small dose of digitalis (1 or 1½ grains by mouth daily without saturation first) for a few days or a week or two before and during and after the operation. This may not be necessary, however; it is always possible to give digitalis intravenously in emergency, and under any conditions it is important to avoid over-dosage, especially to a sensitive person, who may be hurt thereby and whose operative risk may be increased by production of nausea and vomiting or arrhythmia.

Quinidine sulfate is occasionally valuable in the treatment and prevention of arrhythmias which may be serious or fatal in themselves (ventricular paroxysmal tachycardia and ventricular fibrillation) or cause a considerable burden to the heart if it is already diseased (auricular paroxysmal tachycardia and auricular fibrillation or flutter). If arrhythmia is present, it should be controlled as far as possible with quinidine or digitalis or both, before operation. If there is a history of disturbing arrhythmia, especially if recent or frequently recurring, quinidine sulfate (3 grains three or four times a day, after meals and at bedtime) may wisely be given by mouth routinely for a few days before and during and after operation. Even premature beats, ordinarily of little or no importance, may, if frequent, justify the preoperative and postoperative use of quinidine to avoid something worse (paroxysmal tachycardia or fibrillation).

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* It is important to remember that cardiac patients do not withstand parenteral infusions. Therefore, if they are to be given pre- and postoperatively, they should be given very slowly, not more than 40 to 60 drops per minute. Thus they will not embarrass a circulatory system which has little reserve. A postoperative pneumonia can be prevented by judicious observance of this régime.—EDITOR.

Heart block is rare and needs no preoperative treatment unless there are Adams-Stokes attacks, when epinephrine (adrenalin) hydrochloride, 0.5 cubic centimeter in saline or oil, may be given intramuscularly every six to twelve hours just prior to and just after the operation.

Anesthesia must be carefully considered in the presence of cardiac disease, and only expert anesthetists employed. By and large, ether is the preparation of choice, other things being equal, and gas is to be avoided. On occasion, however, other anesthetics, if preponderantly favored by the surgeon, may be safe in the hands of the most expert.

Finally, the closest coöperation between physician and surgeon may be the one factor that permits the risk of a dangerous operation for a cardiac patient whose reserve is low or lacking.

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CHAPTER XXXIX

GASTROINTESTINAL FACTORS IN, AND MANIFESTATIONS OF, RENAL DISEASE

The gastrointestinal tract and the kidneys are interrelated in many ways. This is to be expected from the biologic fact that the gastrointestinal tract represents the entrance and the urinary tract the chief exit for derivatives of the food materials and other substances absorbed from the external environment and metabolized in the internal environment. The rate of absorption and renewal of various substances in the gastrointestinal tract influences the composition of the circulating blood and thereby affects the excretory response of the kidneys. Should the latter be impaired and retention of metabolites result, the gastrointestinal tract, as well as other parts of the body, is bound to suffer from the altered state. Hence, there are numerous gastrointestinal manifestations of organic renal disease. On the other hand, interruption of the free return of the large volume of gastrointestinal secretions to the blood produces serious effects on the circulation and on renal function, which in turn, may be reflected in secondary derangement of gastrointestinal function. Gastrointestinal disturbances can thus play a considerable etiologic role in certain functional derangements of the kidneys. At times, gastrointestinal and renal syndromes are so intimately bound up that it is difficult to distinguish between primary and secondary manifestations. Finally, in the sphere of treatment of renal disease gastrointestinal factors may become of major importance.

I. GASTROINTESTINAL FACTORS IN THE ETIOLOGY OF ORGANIC OR FUNCTIONAL RENAL DISEASE

Probably every disease of mankind has been attributed in some way or another to normal or abnormal function of the gastrointestinal tract. Either the offending agent was ingested and absorbed from the normal bowel, or it entered the circulation as the result of improper bowel function, usually constipation. The term antointoxication has been laid to rest by most authors, but the underlying idea of the formation of poisonous substances during the sojourn of food and bacteria in the gastrointestinal tract still survives. The modern concept of focal infection has naturally extended to the gastrointestinal tract and related organs an important part in the causation of remote disease.

Obviously, a direct connection exists between the absorption of a protoplasmic poison from the gastrointestinal tract and the development of renal tubular degeneration or necrosis as a result of the excretion of the poison by the kidneys. Hence, whether the toxic agent be mercury, lead, bismuth, carbolic acid or diethylene glycol, the occurrence and the degree of renal injury will depend primarily on the amount ingested and on the tolerance of the stomach for the particular substance. Marked irritation of the gastric mucosa and early vomiting may protect the body from absorption of an otherwise fatal dose. The presence of food in the stomach may allay the local effects and permit the onward passage of the poison.

The obstructive or toxic effects on the kidneys of sulfonamides, when administered without adequate fluids, are by now universally known.

Another type of etiologic relation is illustrated by pyelonephritis secondary to typhoid fever. The specific bacteria presumably reach the kidneys *via* the blood stream from the intestinal ulcers. Similar possibilities exist with every type of extensive intestinal ulceration. However, the low incidence of clinical pyelonephritis in persons with ulcerative enteritis or colitis and the frequent occurrence of *Bacillus coli* pyelonephritis in the absence of gross intestinal disease indicate that other factors must operate to furnish the proper background for the renal infection.

If one discards the theory of "autointoxication" because no satisfactory evidence for this process has ever been adduced, one removes many of the alleged gastrointestinal factors in the etiology of renal diseases. Of course, in intestinal obstruction with gangrene and peritonitis, toxic substances undoubtedly enter the circulation and damage the kidneys as well as other organs. Even here the renal injury may be due more to circulatory changes than to direct toxic effects. However, one variety of "autointoxication" deserves serious consideration, if one accepts a certain theory of the pathogenesis of uremia. According to the view sponsored by Volhard and supported by the biochemical studies of Becher,[1] some nervous manifestations of uremia result from retention in the blood of phenols, oxyacids of the aromatic series and other substances derived from the normal bacterial putrefaction of meat proteins in the gastrointestinal tract. Under ordinary conditions these toxic compounds are rapidly excreted by the kidneys and cannot accumulate in the blood in significant amounts. Only in severe renal insufficiency of some duration can a positive xanthoproteic test be obtained on the blood serum. The clinical importance of this type of "autointoxication" is not entirely settled. Certainly its existence in the final stage of uremia should not be used as an argument in support of unphysiologic restriction of dietary protein, particularly meat, at other periods in the course of various renal diseases. It is reassuring to remember that both the intestinal mucosa and the liver are efficient barriers to the usual products of intestinal putrefaction.

The most striking influence of gastrointestinal derangements or diseases is exhibited on the function rather than on the structure of the kidneys. In all conditions associated with loss of fluids from the upper part of the intestinal tract and to a lesser extent from the large bowel, dangerous renal impairment may occur. In pyloric and high intestinal obstruction due to peptic ulcer, cancer or other causes, the patient suffers not only from inability to retain food and fluids but equally seriously from the continued loss of gastric and intestinal juices with their content of electrolytes, and the consequent drain on the blood plasma and the tissue fluids. These changes are rapidly reflected in the behavior of the kidneys, because water for the formation of urine ordinarily becomes available after other requirements have been satisfied. The kidneys, under the abnormal conditions of gastrointestinal dehydration, can now obtain little water and yet must excrete considerable amounts of whatever electrolyte, acid or base, has been left in excess or unbalanced in the blood as the result of loss of other electrolytes from the intestinal tract. Add to the dehydration and abnormal electrolyte composition of the body fluids the disturbances produced by the associated starvation and often increased protein catabolism, and the complex metabolic disorganization becomes obvious. It is not surprising that the kidneys eventually fail to meet the demands, that azotemia and even clinical uremia may develop though the kidneys usually are essentially intact anatomically. General circulatory disturbances due to anhydremia, with poor blood flow in the kidneys, undoubtedly contribute a large share to this picture of extrarenal uremia. An understanding of the sequence of events makes rational and highly successful therapy readily possible.

Less dramatic influences of gastrointestinal events on renal function are exemplified by the fact that the treatment of peptic ulcer with large amounts of alkalis, in one form or another, leads to the clinical syndrome of alkalosis. There may be few symptoms apart from the chemical changes in the blood, or there may be extreme disturbance in the central nervous system. There is usually some impairment of renal function, manifested by a dilute urine, diminished urea clearance and varying degrees of nonprotein nitrogen retention up to the uremic level. In another chapter will be discussed some of the factors in the pathogenesis of alkalosis and renal functional impairment. Suffice it to say here that the absorption of excessive alkali from the gastrointestinal tract in persons with normal kidneys is associated with alkalosis only when there is a simultaneous hypochloremia due to low intake or excessive loss of chlorides. The prevention of hypochloremia is the best prophylaxis for alkalosis with peptic ulcer. It is not unreasonable to insist that every patient should have an accurate estimation of renal function prior to and during the alkali treatment of peptic ulcer.

Another aspect of peptic ulcer concerns renal function. Extrarenal or prerenal azotemia is likely to occur after massive hemorrhage into the upper part of the intestinal tract, particularly if much of the blood is passed on into the small bowel and is not lost in the vomitus. The rapid accumulation of nonprotein nitrogen in the blood under these conditions has usually been attributed to the renal circulatory effects of hemorrhage, shock and dehydration. While these factors undoubtedly can operate during the first few hours to reduce renal function, they could scarcely explain the later prolonged disturbance. Recently, Stevens and his associates[7] have demonstrated convincingly that most of the rise in urea or nonprotein nitrogen in the blood after massive gastrointestinal hemorrhage can be explained on the basis of digestion and absorption of nitrogen from the protein contained in the extravasated blood itself. Furthermore, determination of renal function at the peak of the blood urea retention gave normal values by the urea, inulin and phenol red clearance tests. When normal subjects were fed amounts of blood equivalent to those estimated for a massive nonfatal hemorrhage, a similar increase in their blood urea or nonprotein nitrogen level was found. Evidently the rapid digestion and absorption of nitrogen from blood poured into the intestinal lumen causes a sharp rise in the blood nonprotein nitrogen, just as would the administration of a concentrated solution of urea in a normal person. The term "alimentary azotemia" has been appropriately suggested for this condition.[2] Prolonged shock and low circulating blood volume could aggravate the situation by impairing renal function; also, renal arteriosclerosis or therapeutic alkalosis may be complicating factors in this azotemia.

Another type of gastrointestinal influence on the kidneys is exemplified by the impairment resulting from inadequate dietary stimulation of the kidneys. It is generally accepted by investigators in the field of renal physiology[6] that the amount of protein in the diet has a positive effect on the level of renal function, presumably by inducing alterations in renal blood flow. This is readily demonstrable in the dog and in man, particularly in young children. It is much easier in the adult to depress renal function, as estimated by the urea, inulin or creatinine clearances, by the administration of a low protein diet than it is to elevate function well above the normal level by the feeding of a high protein diet. Ordinarily, there is little danger of consuming a high protein diet. It is too expensive and too much against the average medical and lay superstitions regarding meat and other proteins. However, with many gastrointestinal diseases, the protein intake may be reduced to a subnormal level, or failure of digestion or absorption may lead to inadequate supply of the body with the nitrogenous building stones. This is especially likely with anorexia nervosa, ulcerative diseases of the ileum or colon, sprue and celiac disease, diarrheas due to deficiency of digestive enzymes or to short circuiting of the absorptive region of the bowel by disease processes or surgical resection and a number of other conditions associated with organic or functional changes of the gastrointestinal system. In the absence of a toxic increase of tissue protein catabolism, and with the common reduction in the intake of food, especially of proteins, the blood urea nitrogen may remain at low levels. Renal function, as measured by the concentration test or better by the urea clearance, may be reduced to about 40 per cent of the average normal value in the absence of organic renal disease. Evidently the kidney receives less than its normal blood flow, owing, presumably, to diminution in the normal stimulus of protein metabolism, however that operates. That renal function is not organically impaired is shown by the subnormal, rather than increased, blood urea values and by the return of function to normal as soon as the protein deficit is corrected. Urea itself is not the responsible agent. The actual mechanism of the regulation of renal blood flow and renal excretory function by protein catabolic processes is unknown. Rapid storage of protein in the body may produce the same reduction of blood urea and urea clearance in spite of good intake, digestion and absorption of protein. The kidney seems to respond only to catabolic protein mechanisms, as one would expect in view of the excretory functions of the kidney. What is built up into protoplasm is not simultaneously available for excretion and furnishes no stimulus.

The renal changes resulting from experimentally deficient diet—for example, a diet without choline or methionine—have not yet been recognized clinically and will, therefore, not be discussed.

Whether in addition to these circulatory and metabolic influences there is a toxic effect on the kidneys owing to absorption of bacterial or other poisons from diseased intestinal mucosa is difficult to establish. Certainly in peritonitis secondary to perforating ulcers or intestinal obstruction toxemia is usually assumed to exist; similarly in the peritonitis produced by leakage of bile. The degenerative renal tubular changes observed in these conditions suggest direct toxic damage, but the nature of the active substances is unknown. Ordinarily, disturbances in circulation and in the composition and quantity of body fluids are more important factors in renal impairment, both because they occur early and because they are usually remediable if recognized promptly.

II. GASTROINTESTINAL MANIFESTATIONS OF ORGANIC OR FUNCTIONAL RENAL DISEASE

Organic diseases of the kidney are frequently associated with gastrointestinal manifestations during some part of their clinical course. The phase of the disease during which these symptoms may occur and the nature of the symptoms vary to some extent with the particular renal disease. Since renal insufficiency and uremia form the final stage of all types of organic renal disease—provided the patient does not succumb to hypertensive heart failure, intercurrent infection or accident or a hypertensive cerebral vascular episode—gastrointestinal disturbances usually dominate the terminal stage of many renal diseases. Also, the uremic symptoms referable to the digestive tract may be superimposed on the original or primary gastrointestinal derangement responsible for an extrarenal uremia, producing a clinical picture difficult to analyze and interpret accurately.

Of the symptoms ordinarily attributed to the gastrointestinal tract, the only one not found in renal disease is jaundice. Even in this instance error may arise from the fact that persons with advanced chronic renal insufficiency often present a sallow yellowish discoloration of the exposed skin, but not of the mucous membranes, owing to oxidation within the skin of retained urochromogens. Pain, nausea, vomiting, diarrhea, constipation, loss of weight, gaseous eructation, "indigestion," abdominal tenderness, distention, ascites, hemorrhage, "biliousness," malaise and fatigability—all these common symptoms of gastrointestinal disease may be observed at some time or another and in varying combinations and degrees with renal disease.

Pain.—Acute pyelonephritis and acute diffuse glomerulonephritis are often ushered in by pain, which, though usually located in the lumbar region of the back, may be referred to the abdomen, particularly to the umbilical region, the upper quadrants or the suprapubic area. This is most likely to occur in children, and if nausea and vomiting are present may be misleading until urinary changes and other signs are observed. Severe substernal and epigastric pain will, of course, be found early in mercurial or other corrosive poisoning, with renal manifestations occurring later. The pain of renal calculus or of hydronephrosis may be referred to either upper or lower abdominal quadrant and may mimic various gastrointestinal conditions. Symptoms of bowel distress, spastic constipation or diarrhea or functional "colitis" may be the chief subjective manifestations of a kidney stone and may be aggravated markedly during the actual movement of the stone down the ureter. The more severe manifestations of acute renal colic, including reflex ileus, are well known. However, the possibility of calculous disease, tumor or hydronephrosis of the kidney should be considered more often than it has been for patients with functional gastrointestinal syndromes proving refractory to the usual treatment.

Hypertensive vascular disease is of such common occurrence in the middle age groups that it is bound to be associated with other frequent conditions. It is not always easy to determine whether the connection is an essential one or purely incidental. Thus, it is not uncommon to meet with symptoms of gastric or bowel distress in patients with hypertension. This may be entirely coincidental, owing to nervous, dietary or cathartic factors.

However, persons with advanced hypertension, particularly in the "malignant" phase or in association with cerebal vascular changes, may complain bitterly of abdominal pain of a more or less continuous character, but often aggravated by meals. This distress seems to be along the large bowel and is not responsive to the usual measures. At times it may be definitely combined with a mild renal colic of the typical unilateral distribution and correlated with hemorrhage from the kidneys secondary to arteriosclerosis and arteriolonecrosis. In other instances, the bowel distress so annoying to the patient seems to be a forerunner of a major cerebral vascular accident, usually a hemorrhage. The mechanism of this gastrointestinal pain is not clear, although one is tempted to think in terms of autonomic (parasympathetic) central stimulation. Curiously, in a few patients observed with a history of recent, of old or of still active gastroduodenal (peptic) ulcers, the ulcer symptoms did not recur or assume a dominant role. In general, the development of bowel distress in persons with "malignant" hypertension, even apart from severe renal insufficiency or hematuria, seems to be of bad prognostic import unless the cause is obviously exogenous and responsive to treatment.

Nausea and Vomiting.—While abdominal pain is not prominent in renal disease if one excepts acute infections and obstructive lesions, nausea and vomiting are common. With acute pyelonephritis with or without obstruction, vomiting occurs in association with the fever and pain. Nausea will often be aggravated by the necessary forcing of fluids and usually by the administration of various drugs used as urinary antiseptics. Any obstruction, with resultant hydronephrosis, will make nausea and vomiting more likely.

With acute glomerulonephritis, nausea and vomiting are usually absent when the involvement is mild, but regularly present when it is severe. With the latter type, several factors may operate to produce these symptoms: Reflex ileus may result from acute inflammation and swelling of the kidneys, with distention of the capsule and stimulation of the abundant nerve fibers. When oliguria or anuria develops with acute nephritis and fluids are allowed, vomiting is probably partly secondary to increased plasma volume and to edema of the gastrointestinal mucosa in the first day or two. Forcing of fluids by mouth or parenteral administration of some excess beyond the renal and extrarenal output of water undoubtedly increases the tendency to nausea and vomiting. Also, in the acutely edematous persons, there may be ascites, hydropericardium or pleural fluid to disturb the circulation and function of the gastrointestinal tract. The acute hypertension of most of the patients with severe acute glomerulonephritis may lead to rapid cardiac failure and hepatic congestion and thus to epigastric distress, nausea and vomiting. Also, the changes in cerebral hydrodynamics produced by acute hypertension—the syndrome of hypertensive encephalopathy—are typically manifested in the projectile vomiting of increased intracranial pressure. Finally, after a few days or weeks of oliguria and low renal function, metabolic waste products accumulate in the body fluids, and gastrointestinal irritation will follow from the central or peripheral emetic effect of these substances. It is evident that the differentiation of the various causes of vomiting with acute glomerulonephritis may be difficult; several factors are often combined. Vomiting in the absence of fever, of gross edema and ascites, of headaches and of considerable hypertension is likely to be of more serious significance than when it is associated with one or more of these symptoms, because it is then probably a manifestation of uremia.

With the chronic forms of renal disease, nausea and vomiting occur usually under certain specific conditions. Thus, the person with so-called latent or mildly active nephritis is not susceptible to gastrointestinal upsets except as they are produced by medication or one-sided diets. On the other hand, the chronically nephrotic or edematous patient is likely to have considerable difficulty with food. The saltless diet may lead not only to anorexia but to actual revulsion and vomiting if feeding is forced. This is not merely a psychologic disturbance but probably also reflects the intolerance of an edematous gastrointestinal mucosa, as well as changes in motility and other reflex abnormalities associated with abdominal distention due to ascites. If the patient has to be confined to bed, as is usually the case, it becomes even more difficult to get the food down and to keep it from returning. The use of various diuretics, like the purine derivatives and the acid-forming salts (ammonium chloride or nitrate), leads not infrequently to considerable gastrointestinal irritation. The onset of pneumococcus peritonitis in nephrotic children may be ushered in by vomiting. For some patients, vomiting, or at least regurgitation, may become an easy way to eliminate this or that special but unpalatable diet. All these complications render difficult the task of the physician in attempting to maintain the nutrition of the patient. It becomes necessary to sacrifice some of the drugs and diets to the general interests of the patient and to give him some opportunity to select his own diet from time to time.

In addition to the vomiting of cerebral origin during acute hypertensive nephritis, there are the periodic episodes of nausea and vomiting during the course of chronic hypertensive nephritis or "essential" hypertension. Often, the gastrointestinal symptoms are part of the syndrome of hypertensive encephalopathy with severe occipital headaches, dizziness, visual disturbance and other manifestations. That the vomiting is not necessarily uremic is shown by the absence of marked or even moderate retention of nonprotein nitrogen in the blood and by the evidence of increased intracranial pressure in many of the patients, if examined early in the development of the syndrome. Of course, true uremia and hypertensive encephalopathy may be combined. The vomiting of the late hypertensive "toxemia of pregnancy" is probably also related to a similar cerebral vascular disturbance. In most of these instances, the headache and vomiting are most likely to occur after the night's sleep or after several hours of recumbency with the head in a relatively low position. Measures employed to reduce intracranial pressure or to dehydrate the brain or sedative medication may be effective in controlling hypertensive vomiting. Nausea may be a persistent feature in this condition, but the patient often learns to eat his breakfast after the early vomiting spell.

During the malignant phase of hypertension, there may be local lesions in the upper part of the gastrointestinal tract productive, perhaps, of nausea and vomiting of a peripheral origin. Thus, superficial hemorrhages, erosions and small ulcers may develop in the stomach and duodenum and be associated with epigastric distress, nausea, vomiting and at times slight hematemesis. These lesions may or may not be secondary to arteriolonecrosis in the submucosa. Sclerosis and partial obliteration of larger vessels in the splanchnic area will usually produce more dramatic syndromes, but these manifestations are relatively rare.

The onset of congestive heart failure, usually after several weeks or months of left ventricular insufficiency, is a common episode in the hypertensive types of renal disease. The usual gastrointestinal symptoms of passive congestion then appear, aggravated by the frequently associated renal insufficiency. The latter, in turn, may be increased to a frankly uremic level by the circulatory failure. The diagnostic and therapeutic problems of the combined cardiac and renal insufficiency are often difficult to solve. Coronary occlusion occuring in the course of "essential" hypertension may produce a similar complex clinical picture.

Renal insufficiency, no matter what the underlying abnormality may be, is so typically productive of nausea and vomiting that the physician must consider this possibility for every patient with unexplained gastrointestinal upsets. But it should be emphasized that moderate impairment of renal function, for example to 30 or 40 per cent of the normal clearance values, with the blood urea or nonprotein nitrogen elevated to about twice the normal level, is not ordinarily sufficient by itself to produce nausea and vomiting. Therefore, in the absence of hypertensive encephalopathy or other conditions commonly associated with renal disease, it is always possible that the patient's gastrointestinal symptoms are due to independent or coincidental local disease. Without a complete work-up from this point of view, including *x*-ray examination, serious but still remediable conditions may be passed over. At this point it is worth referring again to the fact that repeated vomiting and restricted intake of fluids from whatever cause may secondarily lead to renal insufficiency of an extrarenal or prerenal type, not always distinguishable from true renal disease on the basis of the presence or absence of urinary abnormalities. In all cases of doubt, the therapeutic test of parenteral administration of saline solution and chemical examination of the blood for the common electrolytes as well as the nitrogenous substances will soon clear up the diagnostic problem.

With chronic renal disease with rather slow progression toward uremia the onset of gastrointestinal symptoms may be insidious. At first the diminished appetite can in some instances be attributed to restricted diet and the patient's whims. Later, however, actual nausea makes its appearance. This is most frequent in the morning, so that breakfast, if forced down, may be vomited, while later in the day the patient may retain his meals. However, as nitrogen retention increases, the nausea becomes more and more persistent and distressing, so that even the sight and smell of food may produce vomiting. At this stage the patient is likely to feel very sick on awakening and to vomit bile-containing gastric contents. Some persons are able to settle the stomach temporarily by deliberately drinking a glass or two of warm water and vomiting promptly—a sort of gastric lavage. Others remain nauseated and miserable for weeks and rapidly waste away. Hiccoughing often adds to the discomfort of the patient.

There is perhaps no more difficult problem in the treatment of gastrointestinal symptoms than the control of uremic nausea and vomiting. Complete gastric rest, parenteral administration of fluids and dextrose in moderate amounts, sedation (morphine may be necessary for extreme manifestations), subcutaneous injection of atropine, in some cases the use of cocaine or another local anesthetic in the stomach and other measures usually have to be tried to achieve some result. If treatment is begun fairly early, it may be possible to tide the patient over a bad period and then gradually return to a bland diet. During the weeks or months of anorexia and loss of weight preceding the more severe symptoms, nutritional deficiencies of various types are likely to develop, though rarely to the point of obvious clinical syndromes. Hence, the possibility of vitamin lack must be thought of and the appropriate vitamins administered, orally or parenterally. Usually, vitamin B_1 (thiamin), vitamin C (ascorbic acid) and nicotinic acid will be necessary. Riboflavin and other members of the vitamin B complex may be added as indicated.

The general irritability of the upper part of the gastrointestinal tract in preuremic and uremic persons of itself precludes the use of highly seasoned foods, alcoholic liquors or coffee, unless the patient can demonstrate his ability to retain them. It is ordinarily wise to allow the patient to make the attempt.

Probably only in the uremic stage of chronic renal disease is restriction of protein in the diet indicated, because at this time the patient is practically unable to handle the solid protein foods or the frequently distasteful milk; because nonprotein nitrogen retention and acidosis are likely to increase and produce worse symptoms and because the higher urea content of body fluids is accurately reflected in the intestinal secretions, with the unfortunate complication that bacterial decomposition of urea to ammonium carbonate yields a potent irritant of gastric and intestinal mucous membranes. Furthermore, some investigators[4] have expressed the belief that certain of the nervous manifestations of uremia are caused by retention of various aromatic compounds derived from intestinal putrefaction of meat protein. All these reasons support the general practice of restricting the protein intake of persons with severe renal insufficiency. This measure also reduces the amount of phosphate and of sulfate released in metabolism and tends to diminish the acidosis. However, the common mistake is to limit protein in the diet without insuring an adequate caloric intake in the form of carbohydrate or fat to reduce the endogenous protein catabolism to a minimum. Unless enough calories are provided, the body protein will be wasted for energy purposes and other losses and the person's nutrition suffer correspondingly. The practical problem of maintaining nitrogen balance on a low protein diet in the presence of nausea and vomiting is no simple one, but much can be done. In the near future, perhaps, intravenous alimentation of balanced diets may become a reality.[3] Certainly, full use should be made of aminoacids, dextrose, saline and vitamins when parenteral feeding is necessary.

To what extent the inorganic or mineral acidosis of severe renal insufficiency plays a role in the nausea and vomiting is not clear, because gross acidosis is such a late manifestation of uremia that many other factors are already active. However, by analogy with other states of acidosis, it may be assumed that nephritic or renal acidosis does irritate the gastrointestinal tract unless the patient is actually in coma. This consideration is of importance from the therapeutic standpoint. Since acidosis in chronic renal insufficiency comes on gradually, and not suddenly as in diabetic ketosis, there may be few gross symptoms, particularly when the patient is in bed. Only chemical examination of the blood will reveal the marked decrease in carbon dioxide and in total base. Complex electrolyte adjustments may follow vomiting, administration of fluids and other events. If alkali treatment is indicated and resorted to, the initial dose should be given intravenously and with proper control of the serum bicarbonate level, because of the local irritant action of sodium bicarbonate on the gastric mucosa and the uncertainty of retention and absorption in a patient likely to vomit. After nausea has subsided somewhat, sodium citrate in small amounts (1 to 4 Gm. a day) may be tolerated by the stomach. Larger doses will usually cause symptoms and may lead to serious alkalosis in the uremic patient, whose kidneys are unable to excrete an excess of alkali. The low serum calcium level of some patients with uremic acidosis and retention of inorganic phosphates may form a background for tetany, to be activated by alkalosis. If there is any doubt as to whether muscular twitchings or spasms of a uremic person are tetanic or not, should be given the benefit of intravenous injection of calcium gluconate in adequate amounts. Calcium lactate, orally, may help reduce intestinal absorption of phosphates and thus diminish the phosphate acidosis of renal insufficiency.

Therapeutic Dyspepsia.—With various types of renal disease there are often digestive disturbances due to medication commonly prescribed. This may become a serious problem, because the physician must then choose between a more or less prolonged period of inadequate intake of food and the desired therapeutic effect, whether it be diuresis, improved circulation, bacteriostatic action on infected urine or reduction of nonprotein nitrogen retention. Many of the drugs used are directly irritating to the gastrointestinal tract—for example, the purine diuretics and mandelic acid. Epigastric or general abdominal distress, gaseous eructations, nausea and vomiting or diarrhea commonly results unless the oral medication is intermittent and given with due regard to the time of meals. Similar local irritation is caused by the large doses of ammonium salts used to acidify the urine in preparation for the use of bacteriostatic or bactericidal drug or as an adjuvant to organic mercurial diuretics. When potassium salts are given in large doses for diuresis in nephrotic edema, epigastric burning and nausea may result. Ordinarily, the intravenous injection of organic mercurial diuretics causes few or no bowel symptoms. In some persons considerable bowel distress and several loose stools may follow, especially after the rectal administration of mercurial suppositories, but usually not severe enough to contraindicate this convenient route of administration. The use of digitalis in treating cardiac failure with renal insufficiency may be rendered difficult by the coincidental nausea and vomiting. Sulfonamide irritation of the gastrointestinal tract must be distinguished from secondary abdominal symptoms due to obstruction of the urinary tract or renal damage by these drugs or their acetylated derivatives.

The increasing parenteral injection of fluids, especially intravenously, is another cause of therapeutic indigestion. While there is no question of the utility and indispensability of this form of treatment, the limits of tolerance of the patient are not sufficiently recognized, especially the inability of the severely impaired kidneys to excrete rapidly an excess of circulating fluid. Various disturbances result, partly general circulatory and partly local intestinal changes, and partly reflex irritation caused by accumulation of the excess fluid in various body cavities. The final effect is likely to be distressing nausea and vomiting. Hypertonic solutions may also cause direct irritation. It is well known that the rate of injection must be carefully controlled to prevent unpleasant reactions. The time of injection in relation to meals and sedatives may be of importance to the patient's comfort or distress.

Diarrhea and Constipation.—Disturbances in bowel action—diarrhea or constipation—are not of special significance in acute renal disease except as an indication of ingestion of some poison, for example, mercuric chloride, or as part of general anasarca, when loose watery stools may make their appearance. Diarrhea is not uncommon at the onset of acute pyelonephritis with fever and may occur with urenia as a symptom of colitis or proctitis.

Acute glomerulonephritis may or may not be accompanied by early constipation. The reduction in food intake in the presence of severe involvement would of itself lead to constipation. Reflex ileus, along with abdominal pain, may be mistaken for intestinal obstruction in some cases of acute hydronephrosis from kidney stones. Constipation may also occur in an annoying form in patients with severe hypertension in the "malignant" phase, especially when cerebral vascular changes are occurring.

Hemorrhage.—Bleeding from the gastrointestinal tract during the course of renal disease is usually not severe and practically never a threat to life except in the presence of advanced renal insufficiency. Hence, massive hematemesis or melena should be suspected as being due to some coincidental gastrointestinal ulceration, esophageal varices or an acute mesenteric vascular accident. An exception would be the hemorrhage occurring after ingestion of a corrosive poison, like mercuric chloride, which results in both direct and uremic ulceration of the colon. The injudicious use of organic mercurial diuretics for persons with severe congestive heart failure and renal insufficiency may also cause intestinal hemorrhage.

Ordinarily, in the absence of uremia, acute glomerulonephritis and pyelonephritis are not complicated by hemorrhage from the digestive tract. In fact, such bleeding in the presence of signs of pyelonephritis should make the physician suspect typhoid fever or one of the infectious dysenteries as the underlying disease. A perirenal abscess secondary to pyelonephritis may perforate into the bowel and give rise to temporary hemorrhage, usually followed by rapid subsidence of the general symptoms. Tumors of the kidney are so situated usually that they rarely invade the bowel to cause bleeding.

With chronic hypertensive disease, apart from coincidental peptic ulcer, pronounced hematemesis or passage of tarry stools occasionally occurs, owing, presumably, to bleeding from an arteriosclerotic vessel. Persons with hypertensive heart failure may have slight bleeding into the gastrointestinal tract as a result of passive congestion. Reference has already been made to hemorrhages occuring during the malignant phase of hypertension. In many patients it is necessary to rule out posterior nasal hemorrhage as the source of the vomited blood. Rarely does the gastrointestinal bleeding produce serious effects on hypertensive subjects unless they are markedly anemic. It is possible for localized periarteritis nodosa in the splanchnic region to cause massive or fatal hemorrhage into the bowel in hypertensive patients.

It is chiefly in the uremic state, and usually in advanced uremia, that severe and uncontrollable bleeding may occur, typically in the form of continuous oozing from various parts of the bowel at a time when the patient is already markedly anemic, with a subnormal platelet count, increased capillary fragility and an aplastic type of blood picture, although the bone marrow may show little change. The exact nature of the bleeding is unknown, but it is definitely not due to ascorbic acid deficiency, nor does it respond to large doses of vitamin C. The possibility of prothrombin deficiency should be considered. Blood transfusions may have little or no effect, and at present there is no satisfactory treatment. In some patients, postmortem examination may reveal enough arteriolonecrosis or uremic enteritis and colitis to account for much of the bleeding. In others, no vascular abnormality is found, and it is assumed that the toxic action of retained waste products on the capillary walls was the etiologic factor. Severe anemia and failure of the bone marrow to respond also probably play a part. It is difficult to understand why some uremic patients bleed markedly and others in about the same general status scarcely bleed at all.

Stomatitis.—Inflammation of the gums, buccal mucosa, tongue and salivary glands was regularly included in the older descriptions of uremia. Years ago it was at times frankly mercurial in origin, because of the prevalent oral use of calomel as a diuretic for nephritic patients. However, severe ulcerative stomatitis now occurs apart from the use of mercury and often terminates in ascending suppurative parotitis, which makes the last week or so of the patient's life miserable indeed. This uremic stomatitis, gingivitis and parotitis are largely preventable by proper hygiene of the affected region. In the terminal stages of uremia, dehydration is common, and the mucosa of the mouth and tongue becomes glazed and covered with thick debris and foul residues of food particles. Salivary secretion may be increased early, but later is much reduced. Trauma readily occurs to the under-surface and margins of the tongue in the semistuporous, often drugged patient. Once ulceration sets in, infection spreads rapidly. Proper cleansing of the mouth, adequate hydration, scrupulous avoidance o trauma and gentle removal of all epithelial debris, particles of food or clotted blood will, in most cases, prevent the development of stomatitis and parotitis. Gingivitis may be impossible to control in previously infected gums. Extraction of the teeth of persons with renal insufficiency has been observed to initiate serious inflammation in the mouth. By and large, uremic stomatitis should become an unpleasant clinical memory of the past, along with uremic colitis.

Gastritis.—The abdominal distress, flatulence, anorexia, nausea, and vomiting of persons with advanced renal insufficiency are to a considerable extent due to the acute or chronic gastritis regularly found in these patients. The frequent decrease or absence of hydrochloric acid in the gastric juice favors bacterial action. The high concentration of urea furnishes a source of irritating ammonium salts. Circulatory and motor disturbances aggravate the condition of the mucous membrane so that the stage is well set for various types of gastric symptoms. In addition, dietary deficiencies may develop because of the anorexia or one-sided diets and probably further impair the function of the gastric mucosa. The irritant action of medicaments has already been alluded to. The resulting complex of symptoms is not particularly specific, as it is often found with other types of gastritis.

Enterocolitis.—Serious involvement of the large bowel, less frequently of the terminal part of the ileum, is observed in patients with renal disease only when they are uremic. It used to be common for symptoms of active colitis to supervene in the terminal stages of renal disease. Nowadays only moderate bowel symptoms are exhibited by the patient with severe renal failure; even at the necropsy relatively little change may be found in the ileum or colon. It seems probable that the old popular method of profuse colonic irrigation, as well as oral administration of strong cathartics, irritated the bowel and washed away the protective mucus, so that the action of bacteria and ammonium salts derived from urea could produce a severe superficial pseudomembranous colitis. The gentler modern treatment of the large bowel has largely removed the annoyance of uremic colitis. There still remains, however, the rather frequent localized proctitis caused by use of rectal thermometers in persons with low resistance.

Peritonitis.—This complication is practically limited to children with the nephrotic syndrome. In the presence of such conditions as suppuration of the kidney, tuberculosis or actinomycosis, extension may take place to the peritoneal cavity. However, this is relatively rare.

The onset of peritonitis in children with nephrosis may be insidious—with some elevation in temperature, possibly vomiting, more than the usual abdominal distention and rarely pain. At times only the fever gives a clue to the change. If some of the peritoneal fluid is aspirated, pneumococci may be demonstrated on smear or culture. It has been shown that the organisms are usually of the same type as those found in the upper respiratory passages of the child.[5] The reason for the common development of peritonitis in nephrotic children is the combined presence of pneumococci in the respiratory passages and of a good culture medium, the ascitic fluid. In adults, this complication is much rarer. Some children may go through several attacks of pneumococcus peritonitis. However, it is often the terminal event in the nephrotic syndrome. Early recognition and proper treatment with one of the sulfonamides should lower the mortality considerably.

III. CONCLUSION

The gastrointestinal tract and the kidneys exert mutual influences on one another, in disease apparently to the detriment of the patient as a whole. However, the initial events in this interreaction may well be processes of compensation for serious disturbance in the one or the other system. Thus, the oliguria and low excretion of chlorides of patients with obstructive vomiting due to stenosing peptic ulcer are really a protection against further loss of body fluids and their contained chloride. Later, of course, the kidney suffers from the disturbed circulation and dehydration and its failure is heaped upon the body's other difficulties. Similarly, the excretion of urea into the intestinal tract of persons with renal insufficiency may be useful early in uremia, but the secondary irritation of the resulting increased ammonium carbonate concentration in the intestinal lumen causes dangerous complications. The partition of the excretion of certain substances, like calcium and phosphate, between the kidneys and the bowels is another illustration of the interdependence of the two systems. In this and similar examples the connection may be merely one of the degrees of absorption or route of supply of a given substance. Thus, if for some reason calcium fails of absorption from the gastrointestinal tract, there will be less excretion of calcium in the urine. On the other hand, if for some reason calcium is being dissolved out of the bony warehouse and increases its concentration in the serum, the urinary calcium output will also be augmented. There must be various and much more complex instances of this relation.

Contrary to earlier opinions, however, the gastrointestinal tract cannot substitute significantly for the renal system, any more than the skin can do so. Therefore, in the treatment of renal diseases, the gastrointestinal tract should be dealt with rather as an absorptive mechanism, on the adequate functioning of which the nutrition and well-being of the entire person depend, than as a drainage canal to be flushed into violent action when the kidneys begin to lag behind with their daily burden. This means gentle treatment by the physician and provision of a diet satisfactory not only for the ordinary requirements of the healthy body but for the extra needs created at times by the loss of such constituents as plasma proteins, specific electrolytes and other substances. The details will vary with the individual case, but the general principle is the welfare of the patient as a whole.

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CHAPTER XL

GASTROINTESTINAL MANIFESTATIONS OF UROLOGIC DISEASE

INTRODUCTION

Of late much attention has been drawn by both internists and urologists to the frequent association of gastrointestinal symptoms with urologic disease, particularly of the upper part of the urinary tract. In the past, and to an extent even now, textbooks dealing with gastrointestinal diseases or genitourinary diseases have paid little if any attention to this interesting and important connection.*

History taking and a careful analysis of symptoms are frequently gone over hastily because of the ease with which radiographic examinations are made and because of the precision of the cystoscope as an examining instrument. History taking should be complete for all the body systems, and just because one is either a urologist or an internist one's attention should not be focused on his particular specialty. This is particularly true of many diseases of the upper part of the urinary tract in which few if any symptoms are present in the genitourinary tract but all are referred to the gastrointestinal tract. Epigastric distress, gaseous distention, nausea, vomiting and diarrhea are frequent in upper urinary tract disturbances.

Disturbances in any part of the urinary tract may cause gastrointestinal symptoms, owing to (*a*) viscerovisceral reflexes, (*b*) mechanical pressure or displacement or (*c*) absorption of toxic products, due to infection or stasis or both or the result of a nephritic condition. The kidney and ureter, being in close proximity to the various portions of the gastrointestinal tract, produce symptoms frequently misleading as to the actual site of the lesion.

With various infections of the urinary tract, acute or chronic, nausea, vomiting and gaseous distention are frequent symptoms. These either are due to absorption of toxic products or result from decreased function of the kidney, with absorption of nitrogenous waste products. In cases of marked decrease of kidney function the intestinal symptoms at times far outdistance any other complaints, with diarrhea being predominant.

The close proximity of the right kidney to the gallbladder, duodenum, pancreas and ascending colon can by pressure on these organs produce symptoms not referable to the kidney at all. This pressure may be due to a tumor, hydronephrosis or enlargement of the kidney from any cause.

Abnormal impulses arising anywhere in the urinary tract may produce digestive symptoms because of the close interrelation of the nerve supply of these two systems. In fact, it is in this group that the majority of cases fall. Tixier and Clavel[11] have called this phenomenon of stimulation of the entire gastrointestinal tract or a specific portion thereof by nerve impulses originating in the retroperitoneal area "the retroperitoneal syndrome." Colby[5] has also called attention to the action of the sympathetic nervous system in the production of viscerovisceral reflexes, so that dysfunction in one organ gives rise to symptoms in other organs.

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* This symptom complex has been described previously by the authors.[8]

Patients are frequently seen with symptoms referable to the gastrointestinal tract that cannot be explained on the basis of pathologic changes in this system. In a number of instances exhaustive study and resultant symptomatic treatment fail to relieve the symptoms. Many of these patients then resort to surgical measures, with no relief of their complaints. Braasch[4] has stated that in many cases of right-sided hydronephrosis the subjective symptoms are rarely referred to the urinary tract, and in these instances the appendix is practically always sacrificed before the renal lesion is discovered. In this group of cases it is most advisable to investigate the urinary tract before any surgical measures is resorted to. Too much stress cannot be placed on this point, because statistics from various clinics show that 15 to 20 per cent of patients with urologic disease had various abdominal operations with no relief of symptoms.[3]

Delay in recognition of urologic disease entities is the rule, and is easily understandable when the symptoms are so frequently referred elsewhere. However, when gastrointestinal symptoms do not respond to treatment after a resonable length of time, then surely the urinary tract should be one of the group of systems investigated. The investigation should be a complete one, both instrumental and radiographic, for one should not rely completely on intravenous urograms, although these at times may be of great help.

NERVOUS SYSTEM CONNECTIONS BETWEEN THE GASTROINTESTINAL AND THE URINARY TRACT

Abeshouse[1] stated that the innervation of the stomach, small intestines, cecum and transverse colon is derived in part from the same source as that of the kidney and ureter. These alimentary organs receive their nerve supply from (1) the vagus nerve, which contains parasympathetic (excitomotor) fibers and (2) the celiac plexus, the sympathetic (inhibitomotor) nerves of which come by way of the greater splanchnic nerve from the fifth to the ninth dorsal segment of the cord and through the lesser splanchnic nerve from the tenth to the twelfth dorsal spinal segment. The remainder of the gastrointestinal tract (descending colon, sigmoid, rectum and anal sphincter) and the lower part of the genitourinary tract have a common nerve supply consisting of (*a*) sympathetic fibers derived from the lumbar segments of the cord and (*b*) parasympathetic fibers originating in the second, third and fourth sacral segments.

Thus, both the urinary and the gastrointestinal tract are innervated both by sympathetic and parasympathetic fibers in close relation with one another, and through viscerovisceral reflexes, disturbances in one organ may produce symptoms in another organ with a similar nerve supply. This mechanism explains the gastrointestinal symptoms produced by urologic disease. Smith[10] has shown that the celiac plexus appears to be the center of reflex action for stimuli originating in the kidney, ureter or posterior part of the parietal peritoneum.

Tixier and Clavel[11] stated that from the point of view of their gastrointestinal effects the renal reflexes may be classified according to the organ in which they predominate. The types are (1) renogastric reflexes (these are motor, secretory and vasomotor; the pyloric sphincter is particularly sensitive to these stimuli); (2) renointestinal reflexes (these sometimes produce spasm and at other times paralysis; the large intestine is particularly sensitive to these reflexes; in the presence of ureteral stones the rectum may show symptoms); (3) renoperitoneal reflexes (producing evidences of peritonitis).

Besides the gastrointestinal symptoms produced by these various reflexes, other symptoms, such as localized muscle spasm or rigidity, may appear. In addition, changes in pulse, respiration and temperature may result from stimulation of the nervous mechanism involved.

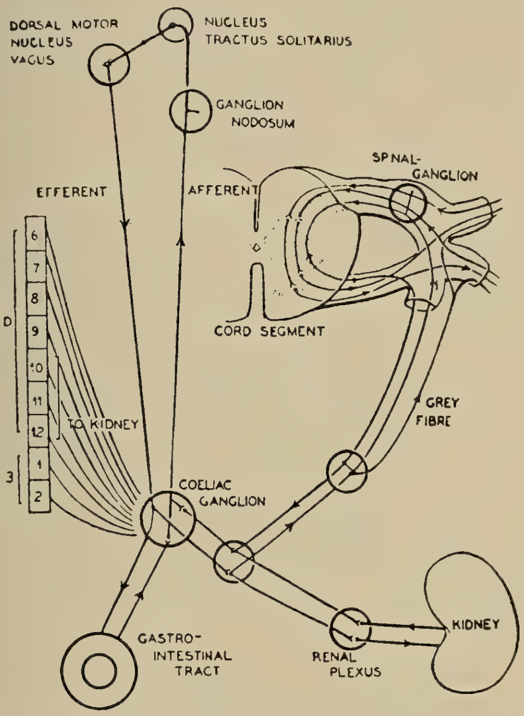

FIG. 172.—Nerve relations between the urinary and the gastrointestinal tract. (Smith,[10] courtesy of *Canadian Medical Association Journal*.)

Lesions within the urinary tract most commonly produce gastrointestinal symptoms as a result of stimulation of various nerve fibers in either the renal pelvis or the ureter. In addition, stimuli may arise from irritation of the mucous membrane of the urinary tract or stimulation of fibers in the posterior part of the peritoneum. The intensity of the symptoms produced varies greatly. Some lesions which would be expected to produce many symptoms produce few or none, and in addition, the individual predisposition of some persons to severe gastrointestinal symptoms is a well known fact.

SIGNS AND SYMPTOMS

No pathognomonic signs or symptoms lead one to suspect urologic disease in the presence of gastrointestinal symptoms. The problem is more a matter of exclusion, the possibility of such an interrelation being kept in mind at all times. A careful history will usually reveal some urinary symptoms, although at times there may be none. From the gastrointestinal standpoint the symptoms frequently simulate gallbladder disease and occasionally ulcer, especially duodenal, and in many cases are treated as so-called colitis. In addition, symptoms referable to the appendix are frequent. The gastrointestinal symptoms of nausea and vomiting are common with any disease of the upper part of the urinary tract. In addition, gaseous distention, belching, heartburn, epigastric distress, constipation or diarrhea may be noted.

The important thing here to remember is that for all patients, no matter how evident their symptoms may be, in the diagnosis of any gastrointestinal lesion a complete and careful urologic history should be taken. If no results are obtained in the treatment, then surely the urinary tract should be investigated.

Illustrative Cases

Case 1.—Mrs. R. F., aged twenty-seven years, was first seen Aug. 29, 1923, by an internist, with complaints of pain in the right side, nausea, lumbar pain, headache and loss of weight. For the past five years she had had pain in the right lower quadrant of the abdomen, which was more or less constant. Appendectomy had been performed four years previously for this complaint. The pain radiated up into the back and to the scapula on the right side. She felt nauseated when the pain was at its height; it never was referred to the pubic region, and she never required opiates for relief. There had been fulness and distention after meals. Noteworthy physical changes were a systolic murmur at the base of the heart and blood pressure of 142 systolic and 90 diastolic. There was some tenderness over the gallbladder region, and roentgenograms revealed a prepyloric spasm in the lesser curvature side of the stomach, which was distinctly tender. Otherwise, gastrointestinal examination gave negative results. She was treated for three years, off and on, by gastrointestinal management, with improvement and relapses. In 1926, with the return of symptoms, a cholecystogram was made, and what was thought at that time to be a pathologic gallbladder was observed. On suitable management there was a return of her previous symptoms, and at this time it was thought wise to investigate the urinary tract. Cystoscopic examination showed no abnormality, except for a freely movable right kidney. Right-sided pyelograms showed the right kidney pelvis in normal position with the patient lying flat on the table and prolapsed down to the crest of the ileum when the patient stood up. The kidney could be easily displaced so that the pelvis was seen over the spine. After much discussion it was thought advisable to do a nephropexy. She was operated on by another urologist. For the last six years the patient has been entirely relieved of all her symptoms and has had no recurrence of her gastrointestinal symptoms.

Comment.—This case illustrates both biliary and gastroduodenal symptoms produced by nephroptosis. In addition, the patient had had an appendectomy performed prior to a correct diagnosis. It is known that in the past many erroneous diagnoses of nephroptosis, with resultant nephropexy, were made. However, today, with more accurate urologic diagnostic measures, there should not result any indiscriminate operations for nephroptosis. An important point to remember is to be sure to take films with the patient upright when doing urographic work, especially for women.

Movable kidney, hydronephrosis and tumors or cysts of the kidney are most frequently misdiagnosed as disease of the gallbladder. Numerous authors have reported jaundice diagnosed as due to cholelithiasis in patients who had movable kidney, and the jaundice proved to be due to the nephroptosis. Rolleston and McNee[9] stated that the peritoneum over the kidney is continuous with that covering the duodenum and the common bile duct, and any undue mobility of the kidney will lead to traction on and narrowing of the duodenum and bile ducts; also there may be a displacement of the gallbladder, kinking of the cystic duct and even a torsion of the bile ducts. In this way the presence of jaundice in cases of nephroptosis is explained. Other conditions, such as tumor or cyst of the kidney or lesions in the perirenal space with pressure on the posterior part of the peritoneum, may produce jaundice.

Case 2.—Mrs. M. H., aged thirty-three years, was first seen on March 4, 1938. At that time she complained of intermittent attacks of nausea, vomiting, diarrhea and left lower quadrant pain. In addition, she had dull left lumbar pain. She had lost some 20 pounds during the past two years. In 1937 she had had a pelvic operation for her complaints, without any relief of symptoms. A complete gastrointestinal work-up was done, but there were no positive findings. Because of her diarrhea, loss of weight and residence in the south, her stool was carefully examined for parasites, but none were found. During one of her severe attacks of nausea, vomiting and left lower quadrant pain she was seen in a typical Dietl's crisis. The patient when lying down would pass large amounts of urine. At no time had she thought it advisable to mention this fact. Urologic examination showed no noteworthy bladder findings. Functional tests on both sides were normal. Retrograde urograms showed bilateral neproptosis, more marked on the left side, and a moderate hydronephrosis on the left side. Nephropexy was performed on the left side on March 25, 1938. Since then the patient has had complete alleviation of her symptoms and has regained some 15 pounds in weight.

Comment.—In this case the symptoms were mainly colonic; however, in a majority of cases symptoms referable to the colon are produced mainly by ureteral lesions because of the close approximation of the ureter to the colon. Numerous authors, especially Hunner, have called attention to the frequent association of gastrointestinal symptoms with ureteral stricture. Many patients with nephroptosis present bizarre gastrointestinal symptoms which are relieved on assumption of the prone posture. In taking the history this fact should be kept in mind, especially for women. Left-sided nephroptosis with production of severe symptoms is rather unusual.

Case 3.—Miss S. G., aged forty-three years, was first seen on Feb. 7, 1928. She complained of epigastric pressure. For the past three or four years the patient had had recurrent attacks of pain in the epigastric and substernal regions, coming on during the day and night, never awakening her and lasting for an hour or so. There were no particular relation to meals and no nausea, vomiting or jaundice. She had, however, excessive belching and passage of gas. There was definite fulness in the epigastrium, and there was a dull area displacing the normal stomach tympany. Repeated examinations of the urine gave negative results. Gastrointestinal examination showed the cardiac end and greater curvature side of the stomach displaced to the right half of the abdomen. The duodenal bulb, when brought into view, was normal.

Plates confirmed the fluoroscopic observation, showing the stomach displaced to the right and the transverse colon depressed into the pelvis. Cystoscopic examination revealed no noteworthy bladder changes. Functional tests on both sides were normal. A left retrograde pyelogram showed the left kidney pushed down toward the pelvis by a mass at the upper pole. In addition, there was a slight degree of hydronephrosis. A diagnosis of solitary cyst of the kidney was made. At laparotomy this was confirmed. The cyst was resected and the kidney left *in situ*. After the removal of the cyst the patient's gastrointestinal symptoms completely subsided.

Comment.—This case is illustrative of the kidney's producing pressure and displacement of various portions of the gastrointestinal tract with gastroduodenal symptoms.

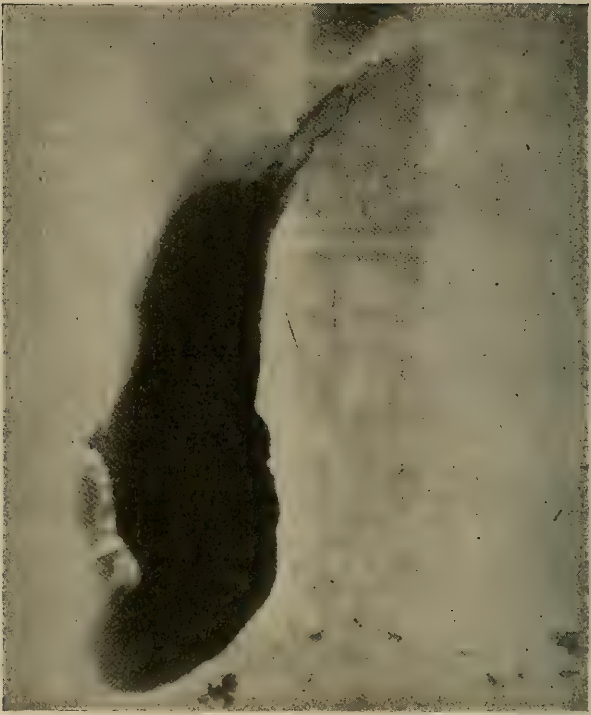

FIG. 173.—Displacement of the stomach to the right of the vertebral column by a large solitary cyst of the kidney (Case 3).

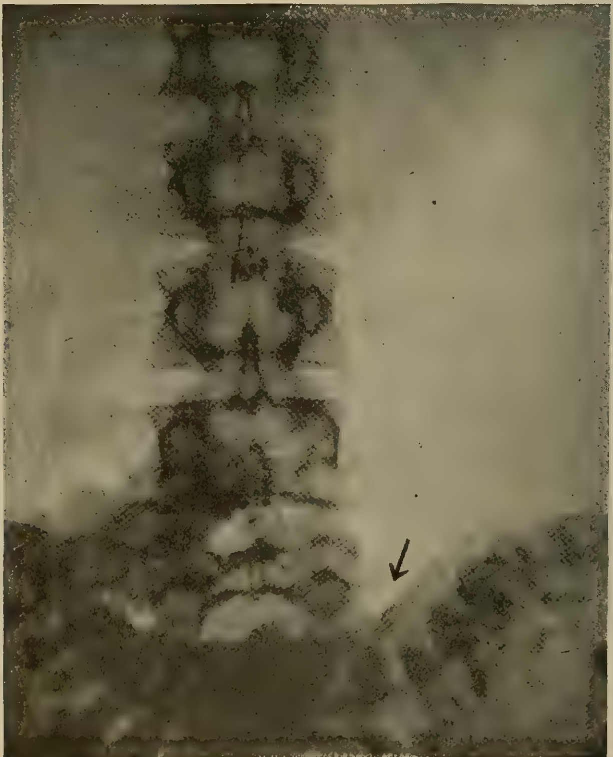

FIG. 174.—Depression of the transverse colon by a large solitary cyst of the kidney (Case 3).

Case 4.—Mr. W. S., aged thirty-six years, complained of epigastric distress, belching and vomiting, the last being present mainly after breakfast. These symptoms had been present intermittently for two years. At one time a diagnosis of duodenal ulcer had been made. He had no pain before or after meals. Ulcer management failed to relieve his symptoms. In addition, he stated that he often noted a cessation of his symptoms on lying down. Prior to urologic examination a complete gastrointestinal study failed to show any pathologic findings. Intravenous urograms revealed a moderate hydronephrosis on the right side, with a slightly abnormal insertion of the ureter. The left kidney showed normal filling. With the patient in the standing posture the right kidney rotated anteriorly, giving the impression of a lateral urogram. After one hour the right renal pelvis was still filled with dye. There was no ptosis of the right kidney.

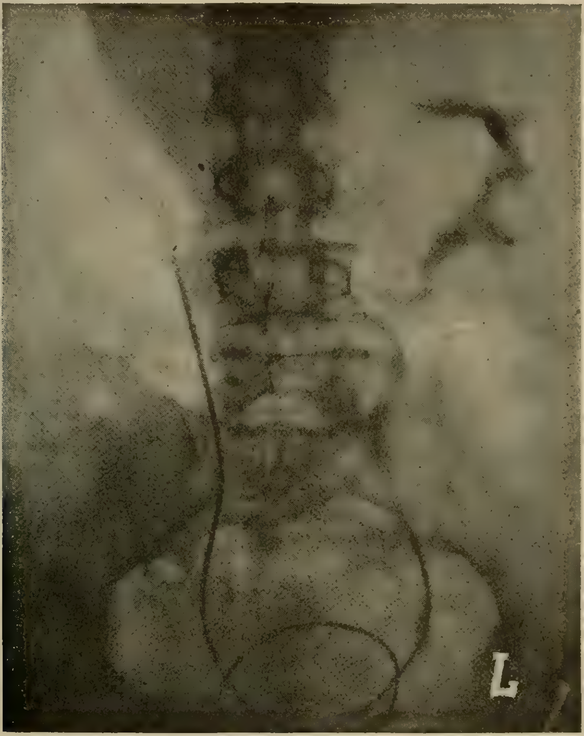

Fig. 175.—Retrograde pyelogram of a solitary cyst of the kidney (Case 4).

Comment.—In this instance the gastroduodenal symptoms were produced by an abnormal rotation of the right kidney when the patient was in the upright posture. In turn, this had produced a moderate hydronephrosis, with marked delay of emptying of the right renal pelvis. Operation was advised to fix the kidney so as to prevent rotation, but this was refused by the patient. He wished to try conservative treatment, so a belt was ordered to produce pressure over the kidney anteriorly, with the hope of preventing rotation. To date, after wearing of the belt for one month, his symptoms have been markedly relieved.

Case 5.—Miss E. S., aged thirty-three years, was first seen March 1, 1928. At this time she complained of upper abdominal pain. During the past twelve years she had had attacks of diffuse abdominal pain. The attacks usually lasted from twenty-four to forty-eight hours and were accompanied with a temperature of

102 F. There was no nausea or vomiting. A great deal of belching occurred, however. Six months before she had had an attack of pain, accompanied with jaundice, which lasted ten days. She had previously been told that she had blood and pus in the urine. Cystoscopy had been done at that time, and a kidney infection was diagnosed. She had been seen subsequently by another urologist, who confirmed this opinion. However, little attention was paid to this finding. During the interval an appendectomy and cholecystectomy had been performed, with no improvement. After this, urologic examination showed a marked fibrous stricture of the lower two-thirds of the urethra. The bladder wall showed numerous areas of coarse trabeculation and marked edema around the right ureteral orifice. Upper urinary tract study revealed no abnormality. Dilation of the stricture produced an amelioration of her upper abdominal symptoms, which has persisted to date. The patient reports for routine dilation.

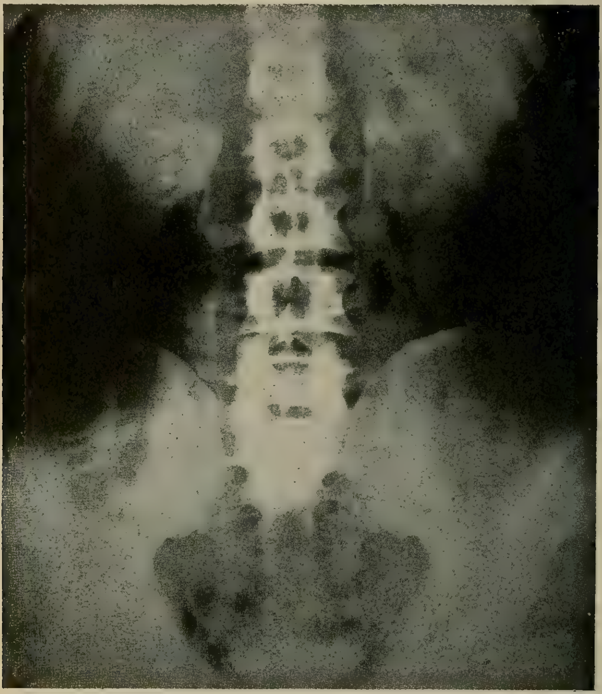

Fig. 176.—Intravenous urogram, showing right-sided hydronephrosis, with abnormal insertion of the ureter (Case 4).

Comment.—In this case the gastroduodenal and biliary symptoms were due to upper urinary tract infection as a result of a urethral stricture—in other words, an ascending pyelonephritis. Various surgical measures had failed to relieve her symptoms. A rather large group of patients, particularly women, in whom definite pathologic changes have been found in the urethra, has escaped the attention of the internist. Folsom, Stevens and others have called attention to lesions in the female urethra producing symptoms of upper urinary tract disease with resultant gastrointestinal symptoms. Urethral changes in females, particularly stricture, are not rare, for if the urethra were examined as a routine during pelvic examinations, the entity would be found rather frequently. Urologically, the changes are those of a definite stricture, usually in the anterior third of the urethra. Here one finds a definite narrowing, and catheterization is done with difficulty, if at all. Passage of a bougie reveals a definite "hang." The back pressure in the bladder results in cystoscopic changes closely resembling those seen with prostatic hypertrophy, the degree depending on the duration of the stricture and the severity of the obstruction. Also in the female contractures and enlargements resembling prostatism in the male may be seen, as well as diffuse polypoid formation at the bladder neck.

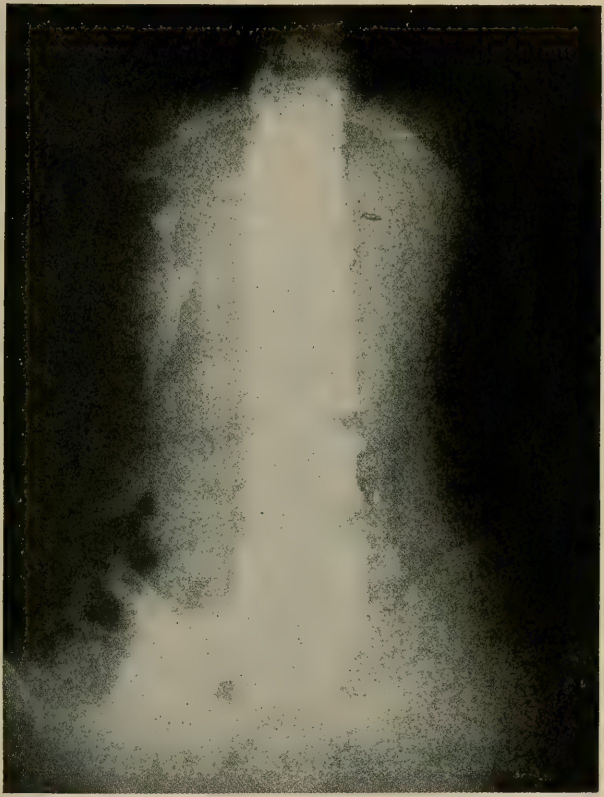

FIG. 177.—Urogram taken with the patient upright, showing abnormal anterior rotation of the right kidney (Case 4).

CASE 6.—Mr. S. L., aged twenty-four years, complained of abdominal distress coming on some two hours after eating; this was associated with frequent belching, nausea and vomiting. Gastrointestinal examination several times gave essentially negative results. At this time appendectomy was advised, in the hope of relieving his symptoms. The patient refused operation and was put on ulcer management. He had one severe attack of epigastric distress resembling that seen with penetrating duodenal ulcer, and when he was seen by his internist, surgical intervention was suggested for a penetrating and possibly perforated duodenal ulcer. At this time the patient suggested that previous attacks had been relieved by prostatic massage. Urologic consultation revealed definitely enlarged and tender seminal vesicles, which on massage showed a large number of pus cells. The upper part of the urinary tract was normal. After massage of his vesicles there was an immediate abatement of his symptoms. During the past five years he has been free of his symptoms after adequate treatment of his prostate and seminal vesicles.

Comment.—The foregoing case is a good example of seminal vesiculitis producing severe gastrointestinal symptoms simulating both appendicitis and duodenal ulcer, and were it not for the fact that the patient remembered that she had received relief following prostatic massage, undoubtedly a laparotomy would have been performed. Goldstein[6] has stated that gastrointestinal symptoms frequently produced by the presence of chronic lesions of the prostate are (*a*) the result of absorption of the toxic products in the prostate or (*b*) a direct result of a urinary obstruction from an enlarged prostate. All patients with gastrointestinal symptoms not responding to ordinary treatment are entitled to a prostatic examination. Acute infections of the seminal vesicles and prostate frequently simulate acute appendicitis. Many patients have had their appendix removed with no relief of symptoms, only later to find that a vesiculitis was producing the symptoms.

Numerous surgeons have had the experience of operating for acute appendicitis only later to find that a ureteral calculus was producing the symptoms. In these cases the absence of fever, the leukocytosis and the presence of red blood cells in the urine would have helped greatly in the differential diagnosis. In addition, when there is any doubt, a flat plate of the abdomen should be taken. Sometimes, however, a correct differential diagnosis is difficult. This is true with retrocecal appendicitis, which may produce ureteritis or periureteritis, with the production of red blood cells in the urine, when it is best to perform an appendectomy to be on the safe side.

Some urologic diseases, particularly renal or ureteral calculi, produce symptoms characteristic of an intestinal obstruction of a paralytic or adynamic type. These are also frequently present after various operative procedures on the genitourinary tract. Nogues[7] maintained that development of a paralytic ileus following operation on the upper part of the urinary tract may be due to (1) mechanical obstruction of the intestines produced by placing a clamp on them; (2) mesenterico-aortic adhesions; (3) obstruction due to torsion or adhesions; (4) toxic manifestations of uremia; (5) traction of the pedicle of the kidney, or (6) action of the anesthetic, particularly a spinal anesthetic, on the intestines. In addition, paralytic ileus is not uncommon after operative procedures on the bladder or prostate.

SUMMARY

The coöperation of the urologist with the internist has brought about a clearer understanding of many obscure symptom complexes that heretofore have not been recognized and—what is more important—that have been treated for many years symptomatically with no relief. Multiple operations are resorted to, and no improvement in the original picture is brought about. The patients are frequently maligned—treated as "neuro" or as hypochrondriacs—and are classified frequently with that all-inclusive diagnosis of "colitis," and yet are no better after the best of talent has had an opportunity to prove its skill.

For obscure abdominal conditions a flat plate of the urinary tract should be taken prior to gastrointestinal *x*-ray examination. This is to avoid overshadowing of renal or ureteral calculi by barium or cholecystographic dye material. A normal film does not always exclude urinary tract disease, because of the presence at times of radiolucent calculi.

Cystoscopic and pyelographic studies are of great importance, and roentgenograms should be taken with the patient in the upright as well as in the prone position in order to rule out nephroptosis. In addition, the prostate and seminal vesicles should be completely examined, particularly in cases of so-called chronic appendicitis. The female urethra deserves special attention in the presence of lower abdominal symptoms.

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CHAPTER XLI

NEUROGENIC DISTURBANCES OF THE GASTROINTESTINAL TRACT

ANATOMY AND PHYSIOLOGY

Local disease processes and functional disorders within the gastrointestinal tract are not alone responsible for its disturbances. Severe alterations in function and ultimately actual morphologic changes are often due to primary diseases of the nervous system. Such diseases may reside within any of several widespread areas of the central nervous system or in the autonomic nerves which flow out therefrom to form the peripheral innervation of the gastrointestinal tract.

Anatomy.—To understand the general significance of neurogenic visceral disturbances, the fundamental principles of the autonomic innervations and their physiology should be understood.[9] The autonomic nervous system is usually considered to consist of peripheral outflows of fine efferent nerve fibers which have synaptic junctions outside the central nervous system and ultimately innervate smooth muscles and glands. As will be seen later, it has a large central component and plays at least an indirect role in the afferent sensory functions of the viscera.

The peripheral outflows are divided into two categories. Their discreteness is only arbitrarily defined, for fibers of both categories mix intimately and undergo synapsis profusely within the peripheral ganglionic nodes. The peripheral orthosympathetic fibers arise from cells in the lateral gray columns of spinal segments within the lower cervical, all of the thoracic and the upper lumbar portion of the spinal cord. These preganglionic fibers enter the paravertebral ganglionic chain by way of the white *rami communicantes* of the anterior spinal roots and undergo synapsis with many secondary postganglionic fibers after ascending or descending the ganglionic chain. Thence fibers within the gray rami pass to the various prevertebral ganglions—the celiac, mesenteric, etc.—and there, many fibers which have not been interrupted in the previous ganglions, undergo synapsis. The postganglionic fibers then enter the walls of the various visceral organs, including those of the gastrointestinal tract. The wide distribution of preganglionic fibers undergoing synapsis with many postganglionic fibers indicates that the innervations of the thoracolumbar outflow, or orthosympathetic system, are diffuse, and not limited to a single organ or organ segment.

The parasympathetic nervous system has several outflows: A cranial outflow through the third nerve innervates the pupil; a bulbar outflow through the seventh, ninth and tenth cranial nerves innervates the upper part of the digestive tract and its derivatives. Especially important for the cranial outflow is the medial portion of the vagus nucleus, which constitutes a medullary parasympathetic center. The sacral outflow from the second, third and fourth sacral segments reaches the large intestine, bladder and genital organs. It is possible that a posterior root autonomic outflow contains vasodilator fibers. The characteristic anatomic peculiarity of the parasympathetic outflows is that they send fibers to individual organs or organ segments and do not undergo synapsis in any ganglion until they reach the visceral organ which they innervate. There a synapse is made within the ganglions on the viscus, and the short postganglionic fiber immediately enters the visceral structure. Thus the parasympathetic innervation is not diffuse but strictly localized.

Physiology.—In general, the orthosympathetic fibers inhibit the gastrointestinal contractions and thus inhibit motility. They also function in contraction of the various sphincters of the tract. The parasympathetic fibers are excitatory to the smooth muscle of the viscera and inhibitory to the sphincters. Such a general statement as to the antagonism of action, however, hardly indicates the true complexity of the physiologic picture. Both systems are excitatory and inhibitory to motility and sphincter control under varying conditions of tonus, and may even be synergic in effect. Rather than strictly antagonistic, the two autonomic systems should be considered as contributing to a functional integration of a complex nature, the exact details of which are being learned only slowly.

There is disputable evidence that afferent vegetative fibers from the viscera eventually enter the central nervous system antidromically along the anterior roots. The majority of visceral sensations are mediated by fine special visceral afferent fibers which run an anatomic course similar to that of all afferent fibers, *i. e.*, enter the posterior root ganglions. Hence they do not truly belong to the sympathetic nervous system. There is some evidence that the vagus nerve carries some type of sensory impulses from the abdominal viscera.

The vagus contains the great parasympathetic innervation to the entire gastrointestinal tract with the exception of the lower portion of the large bowel and rectum, to which the pelvic nerve carries the sacral parasympathetic outflow (S_{2-4}). The orthosympathetic supply to the esophagus arises from fibers of the inferior cervical ganglion (D_{5-6}), that to the stomach from the celiac plexus (D_{5-9}), that to the small intestine from the celiac and the superior mesenteric ganglion (D_{11-12}) and that to the large bowel from the superior and the inferior mesenteric ganglion (L_{1-3}).

Physiologists have known for a long time that gastrointestinal activity proceeds in an orderly and regular fashion even though all the extrinsic nerve supply to the viscera has been severed. Within the walls of the smooth muscle of the tract is a rich intrinsic nerve supply termed the enteric nervous system. It apparently functions adequately without central regulation and without synaptic communication by a process which is vaguely known as axonal reflex action. The clinical importance of this intrinsic neural activity lies in the fact that destructive lesions of nervous connections central to the viscera do not cause disturbances of function, whereas irritative lesions and those releasing one system out of balance are followed by severe functional disorders.

The central autonomic pathways and nuclei are not completely known as yet. The lateral gray columns at various levels form the spinal centers for individually localized segmental activity. The abdominal viscera receive impulses through the splanchnic nerves from centers extending from the fourth thoracic to the second lumbar cord segments. The recto-anal centers are located in the upper lumbar and the sacral portion of the cord. The vagal centers in the medulla are constituted by the dorsal vagus nucleus. Any one or any portion of one of these centers may be damaged by many types of local lesions within the spinal cord or medulla.

Higher Centers.—The existence of general visceral regulatory centers in the medulla oblongata has been suggested since the sugar puncture of Claude Bernard indicated a center concerned with carbohydrate metabolism. The cells of origin of the vagus nerve in the medulla make that structure a parasympathetic center, but there is no evidence that the medulla plays a great role in integration of gastrointestinal function. Integration of reflexes concerned with taste, salivation, chewing, swallowing and activity of the upper part of the digestive tract probably occur in the medulla.

However, there exist in the hypothalamus centers for general regulation of coördinated visceral functions along with more indirect regulation of endocrine glands through connections with the hypophysis. The hypothalamus subordinates the brain stem and medullary and spinal centers and serves as a balancing mechanism between the antagonistic and coöperative outflows of the autonomic system. In the tuber cinereum, especially, lies control of water, fat and carboyhdrate metabolism.

In the cortex, lying close to the corresponding somatic motor cells, there reside areas which influence the autonomic nervous system. These seem to facilitate activity of corresponding somatic structures through changes in blood supply, sweating and temperature. The cortical centers are of importance in integrating emotional changes with visceral activity.

Neural connections of superior, intermediate and lower centers are probably not well defined fiber pathways but short intercalated neurons within the reticular substances. The reticulospinal pathways, pyramidal tracts and some extrapyramidal tracts all probably carry descending autonomic fibers.

Referred Pain.—For long it was questioned whether visceral organs were directly sensitive or whether pain was all mediated through nerve endings in the peritoneum. It is now certain that the viscera are sensitive to appropriate stimuli such as stretching and contraction, by irritation of the endings of visceral afferent fibers which enter the central nervous system by way of the spinal nerves. These fibers pass through the vertebral ganglions and undergo synapsis, like all sensory neurons, in the posterior root ganglions.

The physiologic processes which accompany digestion do not evoke stimuli intense enough to reach consciousness. Spasms and stretchings of smooth muscles beyond the physiologic limit produce stimuli which penetrate the threshold of consciousness. Severe pyloric contraction and dilatation of the stomach are examples of such processes, as well as spasms of smooth muscle accompanying ulceration.

Visceral pains may be deep and apparently located in the viscus disturbed or may be referred to the surface of the body above the viscus or at some distance. Segments of skin distant from and not overlying the diseased organ are involved in the pain because they are innervated by fibers from the same spinal cord segment but have been shifted in embryologic development. The somatic area may be the seat not of pain but of increased sensitivity to stimuli, of tenderness or of muscular spasm.

Several theories explaining referred pain are held today. It has been suggested that the sensory fibers are dichotomous, one branch conducting sensation from the skin and the other from the viscus, and thus pain is referable to both sites on stimulation of either. A more tenable theory suggests that the incoming stimuli from a disordered viscus lower the threshold, cause the spinal segment to be "hyperirritable" and result in increased visceromotor reflex activity, spasms and tenderness. Reflex vasoconstriction of the periphery may affect the cutaneous sensibility of lowering thresholds of sensory end-organs. The fact that local anesthetics injected into the skin in which referred pain exists abolish the pain suggests that the central threshold has been lowered and in the absence of cutaneous stimuli referred pain does not exist. Thus, the most tenable theory of referred pain is that of production of a reflex hyperirritability rather than of a direct overflow of sensory impulses.

CLINICAL DATA

The diffuse netlike intrinsic innervation of the gastrointestinal tract constitutes an enteric mechanism with a reflex integration which seems to suffice for normal coördinated digestive activity. Removal of the extrinsic or the central nervous influences does not disturb gastrointestinal function. Therefore, diseases in man which interrupt the central nervous connections with the viscera are not likely to effect disturbed functions. In fact, those diseases of the central nervous system which are accompanied by disturbances in function are either irritative or result, by destruction of one component of the dual antagonistic outflows, in preponderant action of the other.

Peripheral Disturbances.—The peripheral innervation of the gastrointestinal tract, by which is meant either the extrinsic or the intrinsic nerves within the abdominal cavity, is rarely disturbed, as far as is known. There is, however, a possibility that masses and inflammatory lesions within the abdomen irritate neighboring nerves and plexuses, thus effecting dysfunctions of viscera not directly implicated by the primary pathologic process. It has been a question whether gastrointestinal disturbances following abdominal operations and considered as due to adhesions are not in reality secondary effects of scarring. Operative scars in the viscera, peritoneum or connective tissue may by constant stimulation of implicated nerve fibers cause painful spasms of smooth muscle or direct stimulation of afferent nerve endings. The problem of visceral scars following operations needs further study.

Some authors have suggested that infantile pylorospasm and various sphincter hypertrophies may be secondary to congenital disturbances of autonomic fibers. Tuberculous glands and neoplasms involving the vagus have been associated with gastric dilatation.

McDermid[10] has shown that the presence of hyperalgesia or hyperesthesia of the abdominal wall does not necessarily mean that visceral disease has produced referred pain. The hyperalgesia may be due to disturbances of innervation of the wall itself. In fact, by a cutaneous visceral reflex, disease of the somatic nerve roots or larger spinal nerves may transmit their effects reflexly to the abdominal viscera, causing digestive disturbances. Arthritis of the spine, injuries to the nerve roots, etc., may cause gastrointestinal disturbances ranging from mild nausea to marked ileus. Hyperalgesia or abdominal wall spasm may be difficult to differentiate from a reflex disturbance arising in the viscera. Carnett's[2] simple tests of localizing pressure, pinching, etc., to the wall itself may make a differentiation possible. If the hyperalgesia is of simple root distribution the causation is more clearly neurologic.

Spinal Disturbances.—Spinal cord diseases cause manifold disorders in gastrointestinal function. The most classic example is that of tabes dorsalis with its gastric crises. Here there are severe abdominal pains with hypermotility and hypersecretion of the stomach and usually vomiting. The pain has no relation to food taking. It is sharp, agonizing and continuous or intermittent with only short intervals. With the fluoroscope the stomach is seen to be in profound contraction. A tabetic patient may have abdominal tenderness and rigidity of the anterior abdominal wall, especially after prolonged vomiting. The exact site of the responsible pathologic process is not known, but the recurrent bouts of pain can be relieved only by a bilateral section of the pain-bearing spinothalamic tracts in an operation called cordotomy. The hypermotility and nausea are not relieved by this operation, which suggests that they are of vagal origin. The diagnosis of tabes is, of course, based on anisocoria, Argyll-Robertson pupils, hyporeflexia, lancinating pains, ataxia and sensory changes with a positive Wassermann reaction.

In multiple sclerosis there is frequently seen a type of accelerated evacuation of the stomach accompanied by hyperperistalsis with extremely large gastric waves of contraction. The colon is usually in a hypertonic spastic condition, and even the small intestine shows spasms. Constipation, obstipation and even paralytic ileus may ensue. The diagnosis is made by the presence of ataxic spastic paraplegia, with nystagmus, intention tremor and scanning speech. The responsible lesions are probably medullary, releasing parasympathetic activity from control.

Spinal cord tumors and intramedullary lesions often cause constipation if they implicate the tracts innervating the lower end of the cord. Incontinence results when the sensory fibers are involved. Defecation is a reflex action associated with contraction of the rectum and reciprocal relaxation of the anal sphincter. The stimulus for contraction is a tension on the wall of the rectum, which results in a parasympathetic reflex contraction effected by the pelvic nerve. Voluntary control is exerted only over the external sphincter. In spinal shock due to sudden complete lesions of the cord the mechanism is destroyed for a time, to reappear in an automatic form similar to the automatic bladder. Cutaneous stimuli over the perineum will then initiate rectal evacuation. Further description of various diseases of the spinal cord resulting in visceral disturbances would be only repetitive. Any pathologic process will produce the same symptoms, no matter what its nature, if it involves appropriate structures.

Although no pathologic process has been seen under the microscope in Hirschsprung's disease, or megacolon, there is at least a disturbance of the autonomic balance of the lower bowel. The disorder occurs in children. Relief is obtained by lumbar ganglionectomy at the second, third and fourth lumbar segments, the inhibitory nerves to the large bowel being cut.

Gauss[5] has pointed out that three main types of gastrointestinal disturbance arise from lesions of the higher levels of the central nervous system as follows:

1. Dyspepsia with abdominal pain, nausea, vomiting, morbid hunger, capricious appetite, cramps and hyperperistalsis, from irritative lesions of central parasympathetic nervous centers or their release from inhibitory control.
2. Paroxysmal attacks of peristaltic activity, nausea, vomiting, salivation, defecation and abdominal pain, in epilepsy, migraine, tabes, etc.
3. Erosions of the gastric and duodenal mucosa.

Medullary Disturbances.—Medullary syndromes involving the gastrointestinal tract are not well known. Integration of the activity of the upper part of the tract occurs at this level to some degree; at other levels probably the diencephalon and cortex are more concerned. Disturbances in the complicated swallowing reflexes may result from any lesion involving the glossopharyngeal or vagus nuclei or the fiber paths innervating them from above. Vomiting is a medullary reflex and may arise from irritation of the vagal medullary nuclei. Lesions of any type may produce this symptom. It is particularly significant in the localization of neoplasms about the fourth ventricle without increased intracranial hypertension. Such tumors are more frequent in children than in adults and must be suspected in all cases of so-called cyclic vomiting. The manifestation is frequent and has little value in localization in cases of generalized intracranial hypertension due to secondary irritation of the medullary centers. Sialorrhea is a common symptom in parkinsonism and probably indicates a release of the salivary centers from higher inhibitory control.

Diencephalic Disturbances.—Many years ago Rokitansky developed a theory that peptic ulcers are neurogenic. Cushing[3] has recently revised this theory on the basis of clinical evidence associating neoplastic lesions of the diencephalon and gastric erosions. Beattie and his co-workers have been able to produce mucosal ulceration by stimulation of the vagi. Stimulation of the vegetative nuclei of the hypothalamus by intraventricular injections of pilocarpine or pituitrin results in gastric hyperactivity, hypertonicity and hypersecretion. More exact data[4] indicate that stimulation of the anterior (parasympathetic) part of the hypothalamus results in increased gastric motility, and stimulation of the posterior (orthosympathetic) portion results in decreased motility.

Clinically, tumors of the third ventricle are most frequently associated with gastric ulceration, although neoplasms of the ventricle also have been described with this disease.[11] Apparently, wherever a strong central parasympathetic excitation is produced, ulceration may develop. This results from spasmodic contraction of the muscularis and local spasm of mucosal vessels, producing ischemic or hemorrhagic infarcts. Keller has shown that hemorrhage from the mucosa depends on the integrity of the orthosympathetic fibers.

In Opper and Zimmerman's[12] series of neurogenic gastric erosions, 16 of 21 primary lesions were in the diencephalon, 2 in the midbrain and 3 in the cortex. The pathologic process was meningitis, hemorrhage, softening encephalitis, tumor or softening.

It is probable that under normal conditions the parasympathetic appartus is likewise strongly affected by cortical or psychic influences.[8] As a result, there may be a direct stimulation of the tuber or its descending fiber tracts, or—what theoretically amounts to the same thing—a functional release of the vagus from paralysis of antagonistic sympathetic fibers, leading to hypersecretion, hyperchlorhydria, hypermotility and hypertonicity, which are especially marked in the pyloric segment. Spasmodic contractions of the musculature, possibly supplemented by local spasms of the terminal bloodvessels, produce small areas of ischemia or hemorrhagic infarction, leaving the overlying mucosa exposed to the digestive effects of its own hyperacid juices.

Vonderahe[13] has shown that in patients dying from peptic ulcers there are central hemorrhagic lesions, especially in the medulla in the region of the dorsal vagus nucleus. He expressed the belief that these are produced by afferent reflexes from the primary ulcerous lesion. How they are caused he could not say. They may account for dizziness, weakness, excessive perspiration and tachycardia of ulcer patients.

Cortical Disturbances.—Neurologists have known for long that in many cases of epilepsy the aura is a sensation of gastrointestinal distress. Frequently the attack is ushered in with evidence of gastrointestinal spasm. These sensations arise from Jackson's third or highest level of the nervous system, but it has not been known until recently that the cortex contains representation of the autonomic nervous system.[6] Reference has been made to the old work of Bechterev, who found that excitation and inhibition of the pylorus and stomach can be obtained on cortical stimulation.

Recently Watts[14] obtained intestinal movements from stimulation of area 6 of the prefrontal cortex. Sheehan produced gastric inhibition from the same area. Ablation of the frontal lobes was followed by disturbances of motility and secretion of the gastrointestinal tract, leading at times to intussusception and fatal obstruction, with marked abnormal hunger. Motility has been demonstrated to be markedly increased by x-ray examination. Marked hunger is greatest when the premotor area is ablated.

Removal of both frontal lobes results in hyperactivity of the stomach, often with pyloric spasm. Erosions of the gastric mucosa and ulcerous lesions often accompany this hypermotility. Cerebral lesions in the frontal lobes associated with bulimia, or morbid hunger, have been described clinically, especially traumatic lesions; this manifestation probably results from gastrointestinal hypermotility.[15] Epileptic attacks are often preceded by gastrointestinal auras and abnormal movements of the tract.

Migraine is usually associated with gastric symptoms, nausea and often vomiting. The time of appearance and duration vary in each individual. Abdominal migraine[1] has been described frequently and consists in paroxysmal severe abdominal pain without physicial evidence of intra-abdominal disease. Severe dysfunctions of the gastrointestinal tract, such as gastric atony, anorexia, vomiting and constipation, are often present. It seems likely that migraine is produced through a dysfunction of the vegetative nervous system. Correspondingly, ergotamine tartrate relieves the attack or aborts it. Whether the seat of the primary disturbance is the cortex, the midbrain or the medulla is not known.

The syndrome of dyspepsia, abdominal pain, hyperperistalsis, nausea, vomiting, etc., may arise from a destructive lesion of the autonomic premotor areas, releasing from inhibitory control the activity of lower parasympathetic centers. The nature of the lesion is not specific. Congenital aplasias, birth injuries, neoplasms, inflammations and traumatic lesions may all, if they involve the appropriate area, result in the same syndrome. Differential diagnosis is based on the entire neurologic picture.[7]

Surgery.—Operations on the autonomic nervous system are now frequently performed and are of value in some disturbances of the gastrointestinal tract.

Severe meteorism and paralytic ileus may be relieved by spinal anesthesia, causing a blocking out of inhibitory or orthosympathetic fibers. For Hirschsprung's disease relief is obtained by severing the preganglionic and postganglionic fibers of the second, third and fourth lumbar ganglions. This abolishes inhibitory orthosympathetic action. Pain in diseases of the lower bowel may be relieved by cutting the hypogastric and mesenteric plexuses or the presacral nerves.

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CHAPTER XLII

PSYCHOSOMATIC DISTURBANCES OF THE GASTROINTESTINAL TRACT

Introductory Remarks.—Like all vegetative processes, the alimentary functions are influenced by emotions—that is to say, by the activity of the higher integrating centers of the central nervous system. There are emotional influences which are normal and belong to the healthy functioning of the gastrointestinal tract, such as the secretion of saliva and gastric juice on psychic stimulation when the organism is exposed to the sight or smell of food. Emotional stimuli, however, may have also a disturbing influence on alimentary processes: on the appetite, swallowing, digestion and elimination of waste products. A temporary disturbance of any of these functions may occur in any healthy person under the influence of acute anxiety, rage, disgust or other emotional upheavals. Only when such an emotional disturbance is chronic does one speak of a *gastrointestinal neurosis*.

THE DISTURBANCES OF THE APPETITE AND EATING

Psychology of the Nutritional Process.—There is no other vital function which from early life on plays such a central role in the emotional household of the organism as eating. The first relief from physical discomfort the child experiences during nursing, and thus the satisfaction of hunger becomes deeply associated with the feeling of well-being and security, while the fear of starvation remains during later life the nucleus of insecurity (fear for the future), even though actual starvation is not common in this civilization. In severe psychosis (melancholia) the fear of starvation is often a central issue and is openly expressed by the patient. It is not less common in many psychoneuroses, although the patient may not so freely verbalize it. Apart from the sense of security and insecurity, feeding is deeply associated with the feeling of being loved. For the child to be fed is equivalent to being loved; in fact, the sense of security associated with satiation is based on this emotional equation (*oral receptiveness*).

Another emotional attitude of fundamental importance, which already in early infancy becomes linked with eating and hunger, is possessiveness, with all its implications, such as greed, jealousy and envy, because for the child possession is equivalent to bodily incorporation. The thwarting of this possessive tendency and of the wish to receive leads to aggressive impulses, to take by force that which is not given, to take away from others something which the child wants. Thus, biting becomes the first manifestation of hostility (*oral aggression*). It is only natural that these possessive aggressive impulses all centering around oral incorporation should become the origin of the first guilt feelings as soon as the moral feelings begin to appear and the conscience develops. This explains why the psychoanalysis of neurotics who are suffering from various forms of eating disturbances so commonly reveals underlying guilt feelings as the central emotional issue.

Another important emotional connection is that between suckling and pleasure sensations localized in the mucous membranes of the lips and tongue. It is most probable that the infant experiences its first pleasure sensation in connection with suckling, and tries to reproduce the feeling by thumb sucking. These early oral pleasure sensations may be considered as the forerunners of the later genital excitations. In the form of kissing this early libidinal role of the mouth survives in adult life.

To summarize: During early infancy the wish for love, the striving for security, the feeling of insecurity, possessiveness, greed, jealousy and envy all become deeply linked with the hunger drive and the process of nutrition. This explains the important role of emotional factors in disorders of the alimentary functions. Whenever the aforementioned emotions become repressed, and thus blocked from being expressed by voluntary behavior, they sustain a permanent tension and *via* the vegetative pathways may exert a chronic disturbing influence on the different phases of the alimentary process. The asocial, aggressive nature of these emotions makes them particularly apt to create conflict with the environment and consequently to become repressed. The physical pleasure sensations connected with the early forms of nutrition (sucking) explain the frequent emotional disturbances of the nutritional functions when the adult mature sexual functions are inhibited by conflicts. These repressed sexual cravings are expressed regressively by the feeding process, and their rejection manifests itself in eating disturbances.

The knowledge of these few fundamental psychologic facts is necessary for the understanding of the emotional background of neurotic eating difficulties. It must be emphasized, however, that the complexity of the psychic life prohibits rigid schematic generalizations; each individual case must be understood on its own merits. Also, one must be warned against pedantic clinical classifications. In the following material, for practical reasons, the usual clinical grouping of cases will be retained in general but not rigidly applied.

Eating Inhibitions.—**Anorexia Nervosa.**—Periodic or chronic loss of appetite is a common occurrence in different forms of psychoneurosis and psychosis, particularly in reactive depressions, during the depressive phase of manic-depressive psychosis and in schizophrenia. When the loss of appetite is the outstanding symptom and no major psychosis is present, the diagnosis anorexia is often made, although this symptom is only the most overt manifestation of a neurotic disturbance of the total personality. The practical importance of the symptom may make such a diagnosis excusable. With severe disease the patient may lose considerable weight and become seriously emaciated. Women, especially girls after adolescence, show this symptom more often than men. A differential diagnosis from Simmonds' disease, where the disturbance of appetite is a secondary result of a pituitary abnormality, is important and not always easy. In both conditions various starvation symptoms appear, such as low metabolism, disturbance of sugar metabolism and often amenorrhea. Careful psychiatric anamnesis is one of the indispensable diagnostic criteria. Recently, Richardson[29] emphasized the difficulties of differential diagnosis, the rarity of Simmonds' disease and the relative frequency of anorexia nervosa. It must be borne in mind also that pituitary dysfunction may be present without pronounced structural changes. Rahman, Richardson and Ripley[28] found, for example, that in some cases amenorrhea preceded anorexia. These authors also mentioned continuation of subnormal ovarian function after recovery from the anorexia. Although they called anorexia nervosa primarily a neurosis, they admitted the possibility of its combination with an endocrine disturbance. On account of the fine and complex interaction between psychic and endocrine functions, it is futile to try rigidly to establish the primary factor. In a girl, aged twenty-eight years, with severe anorexia nervosa, whom I recently observed, the amenorrhea developed secondarily to starvation, and the menses returned after recovery. Yet, gynecologic examination showed an infantile uterus. Rahman, Richardson and Ripley[28] found, in a total of 12 cases, 4 of undeveloped and 5 of atrophic uterus. Possibly subgonad types are more inclined to this condition.

The stubborn refusal of the nipple by certain infants right after birth may be considered as the earliest manifestation of anorexia. In such cases one may speak of a resistance of the organism against the new adaptation required by the changed life conditions after birth. Certain individual organisms are less flexible in the transition from intrauterine to postnatal existence. Icterus neonatorum is another example of tardiness in adjustment to extrauterine life wherein the liver continues its intrauterine type of functioning.[11]

Careful psychiatric examination of all adults and older children in whom the loss of appetite is not the secondary result of some organic condition reveals the underlying emotional factors. A great variety of neurotic trends can be observed even by superficial psychiatric examination. Rahman, Richardson and Ripley[28] mentioned obsessive, depressive, schizoid features and certain compulsive character trends, such as perfectionism, stubbornness, over-conscientiousness and neatness—moreover, insecurity, sensitiveness and over-ambitiousness. Recently also Richardson[29] and Farquharson[14] emphasized the presence of psychoneurosis as the primary cause. The earlier authors, like Gull[18] and Lasègue,[22] already clearly recognized the psychologic factors as of primary etiologic significance, but the relevant psychodynamic factors could be uncovered and described in detail only by the introduction of the psychoanalytic technic.

Psychoanalytic observation shows that unconscious aggressive possessive impulses, envy and jealousy play, as a rule, the outstanding causative role. These impulses, if inhibited by the conscience, may lead to severe inhibition of eating. It is easy to understand that since eating is a gratification, a guilty conscience, although unconscious, may disturb the appetite as if the patient would not grant himself the pleasure of satiation. Fasting is a common form of repentance to appease the conscience. In this connection it is noteworthy that before anorexia sets in many patients shown an extreme interest in food, sometimes pronounced bulimia.[7]

Another equally common psychologic finding is an unconscious spite reaction. The patient behaves through his symptom like a pouting child who does not eat in order to force the parents to pay special attention to him and to make them worry. The following case may demonstrate the most common emotional factors underlying nervous anorexia:

In a girl, aged eight years, a severe anorexia developed during the summer vacation. The child refused practically all food, and every meal was the occasion of violent scenes, in which the child was forced to swallow a few bites. She lost weight and after a few weeks showed clinical undernourishment. The pediatrician who was consulted prescribed the usual roborants and thoroughly overlooked the emotional factors. After the child's confidence was won, it was not difficult to uncover the emotional background of the condition. The child had a younger sister, at that time two years old, who was fed by a nurse, usually in the presence of the mother, at the time that the patient ate. The psychiatric interview revealed that the older girl had experienced strong jealousy of her younger sister. This little intruder absorbed all the parents' attention. It became evident during the psychiatric interviews that the child's refusal to eat was motivated first by her wish to capture in this way both the nurse's and the mother's attention and direct it away from the little sister to herself. By her stubborn symptom she thoroughly succeeded in doing so. The second motive was a guilt reaction. She wanted to receive all the love, to take away everything from her little sister. Her refusal to eat was at the same time repentance for this envy. The third factor in her anorexia was spite toward the parents, revenge for giving all the attention to her younger sister. A few psychiatric interviews, in which all these emotions poured out dramatically, and a change in the management of the family life promptly eliminated this dangerous symptom. The older girl, instead of having her meals together with the younger one, was taken by the parents to the hotel restaurant for her meals, which she consumed with her parents. Thus, she was given a premium for being the older one, which helped her accept the fact that the younger sister necessarily received more active attention from the parents. Now enjoying the advantages of being the older child, she could more readily renounce the privileges of the baby.

In most adults the same emotional factors can be discovered, although in a more complicated combination. The oral aggressive and receptive tendencies often become erotized and connected with fantasies of sexual practices such as fellatio and cunnilingus. The association of the hunger drive with sexual impulses which are objectionable to the conscious personality also may lead to eating difficulties.[16] In the deep emotional layers such erotic fantasies are a constant finding. Eating is connected also with pregnancy fantasies according to the most common fantasy patterns of childhood and early adolescence, namely, that impregnation takes place orally. Unconscious pregnancy wishes and their fearful rejection make up one of the most common emotional fantasies found contributing to eating difficulties in young girls. In other cases coprophilic tendencies may enter into the picture.[42]

Other Forms of Neurotic Eating Difficulties.—Some patients experience no loss of appetite, but feel embarrassed and inhibited in attempting to eat in the presence of other persons. Not uncommonly young girls cannot eat in the presence of men to whom they have an emotional attachment. Here, the eating disturbance is less generalized, appears only under highly specific conditions and is not connected with the lack of appetite. In spite of being hungry, the patient feels inhibited at eating and feels great embarrassment and fear. Mostly unconscious sexual fantasies with aggressive connotation (oral castrative wishes) plays an important role.

The following history is that of a patient treated in the Chicago Institute for Psychoanalysis by Dr. Leon Saul:

An attractive girl, aged twenty-six years, complained of complete inability to eat in public for six years, because of embarrassment, anxiety, nausea and faintness. This seriously handicapped her social life and her relations with men. She was the oldest of seven children. The father soon gave up all efforts to support the family, which sank into poverty. The patient remained overtly cheerful and generous and was soon even earning money, but she unconsciously resented bitterly the mother's repeated pregnancies by the lazy, dependent father, which further deprived her of her mother's attentions and increased her burden by bringing more mouths to feed. She liked to express her feelings by references to eating and food. For her the most touching expression of love was a gift of food, and when in her dreams she attacked people it was by biting. Her repressed bitterness against her mother resulted in a pervasive sense of guilt. This guilt attached for specific reasons to eating and sexuality, both of which were in consequence inhibited. The eating phobia began when she was taken to dinner by a boy of whom she thought her mother disapproved. She could eat freely only what her mother served her at home, for then she was doing only what her mother urged; she had her mother's attention and love, and her resentment and guilt were reduced.

Therapy.—In both the more generalized anorexias and the more specific neurotic eating inhibitions, the cause may be found by psychotherapy. Expert handling is indispensable. Inappropriate psychotherapeutic means, such as aggressively forcing the patient to eat, may be just as dangerous as artificial feeding. The patient's self-imposed fasting is a means of relieving deep-seated guilt feelings, and the breaking of the symptom without systematic psychotherapy may provoke even more violent self-destructive tendencies, such as attempts at suicide.[29] The use of drugs or insulin injections can be considered of only symptomatic value.

With smaller children a few psychiatric interviews and changes of management may be helpful, while most adults require systematic prolonged interviews. Psychoanalysis seems to be the most promising approach, but systematic investigations are still lacking. In general, cases of specific eating inhibitions are more easily handled than those in which chronic loss of appetite is the predominant symptom. These latter cases present some of the most difficult psychotherapeutic problems.

Bulimia.—While in anorexia the appetite is disturbed by unconscious emotional factors, in bulimia it is exaggerated. It is important before making the diagnosis of psychogenic bulimia to exclude organic factors. In certain endocrine disturbances, such as hyperthyroidism, the appetite may be exaggerated as a secondary result of the increased metabolism. In psychogenic bulimia, the increased hunger is not the expression of the organism's increased need for food, but eating because a substitute gratification for frustrated emotional tendencies which have basically nothing to do with the process of nutrition. The abundance of different emotional factors has been described by psychoanalytic authors, by Wulff,[44] Schmied,[31] Coriat,[10] Benedek[7] and others. The most constant and significant fact seems to be that in all cases the disturbance of eating is a reaction to emotional frustration. An increased craving for love and aggressive tendencies to grab or to possess form the unconscious basis of the paradoxical appetite. Also unconscious feminine sexual tendencies, pregnancy fantasies and castrative wishes usually play a central role. The repeated observation of bulimia in cases in which anorexia later developed shows the close relation between the two conditions.

Therapy.—As for all psychogenic disturbances of the appetite, so for this, only psychotherapy will reveal the cause. The aims of the therapy are to bring into consciousness the repressed emotional tensions and to find for them adequate and acceptable expression in human relations. Like all psychogenic disturbances of the nutritional process, bulimia is only one symptom of a general neurotic disturbance of the total personality.

Nervous Vomiting.—While in anorexia the incorporative function is inhibited, in nervous vomiting the incorporated food cannot be retained by the patient on account of emotional factors. Psychoanalysis in such cases as a rule uncovers intensive feelings of guilt, motivated by aggressive, grabbing, incorporating tendencies. The nervous vomiting is the expression of these guilt feelings. It corresponds to the tendency to return what the patient incorporates in his unconscious aggressive fantasies. Whereas the patient with anorexia cannot take any food because of guilt feelings, the vomiting patient has to return already incorporated food on account of the aggressive symbolic significance of the eating act.[15] This mechanism has been clearly demonstrated by Levine[23] in a case of chronic vomiting. Also Bond[8] referred briefly to a case of neurotic vomiting in which guilty conscience was a most conspicuous feature. Rejection of unconscious pregnancy wishes is another common tendency.

The following report is the history of a psychoanalytic patient of Dr. J. Masserman, who consulted me in behalf of his patient.

An intelligent middle-class girl, aged thirty years, came to analysis with the complaint that for the preceding twelve years she had been subject to menstrual disturbances, food sensitivity, some anorexia and particularly nausea and vomiting whenever she attempted to have social contacts with men outside her own home. The patient stated, moreover, that her illness had forced her to give up many desired recreational and cultural pursuits and had almost abolished all hopes of marriage. Psychoanalysis revealed that the patient, since her earliest recollections, had been dominated by her possessive, ambitious and at times tyrannical mother, whose favor the patient had attempted to insure in turn by professed personal devotion, by struggles for scholastic and musical achievement and later by financial support of the family. However, the patient's hoped-for security in her mother was threatened during late childhood when the mother, jealous of the favoritism shown the patient by her kindly but ineffectual father, openly began to reject her and to favor her three elder sisters. Unfortunately, the patient reacted to the trauma with an even greater fixation of oral dependence on her mother and a renunciation of all instinctual strivings that she feared might increase her mother's hostility. Developing emancipatory social and sexual urges thus early became inhibited. This inhibition, in line with the patient's infantile fixation on her mother, assumed the typical form of disturbance of the nutritional act: the mother being the original feeding person, guilt and fear felt toward the mother led to a rejection of the incorporated food. For example, the patient remembered that even at the age of ten she had vomited when a boy brought her food at a party. Concurrently the patient began to fail in her school work, musical studies and occupational adjustments and thus acted out her ambivalent attitude toward her mother by thwarting the latter's ambitions. Five years before the analysis, at a time when the patient's guilt and anxiety were increased by the disturbing attentions of a suitor, the patient's menstrual disturbances, anorexia, nausea, food sensitivity and vomiting increased to such an extent that she lost about 28 pounds in a few months and was forced to enter a diagnostic clinic. The physical, laboratory and roentgen findings were, however, normal, and the patient was advised to discontinue all medication and to lead a more active and normal life. Significantly, the patient misinterpreted this advice to mean sexual indulgence and therefore, after obtaining her mother's explicit consent and active coöperation, arranged a liaison with her employer's son. During the seven months that this affair lasted the patient's symptoms improved, although she remained more or less sexually frigid and continued to find it difficult to eat in the presence of her paramour. When, however, he finally deserted her to get married, her neurotic symptoms reappeared, and the patient, giving up all further attempts at heterosexual adjustments, returned to live with her mother. During the first year of a psychoanalytic treatment, the patient, with great difficulty, acquired some insight into her extreme dependence on her mother and her anxiety-ridden renunciation of oral incorporative, aggressive and genital desires. At the present writing, the patient has enlarged her extrafamilial, social and heterosexual activities and has experienced only an occasional return in mild form of her previous symptoms.

Nervous vomiting, like all neurotic symptoms of the gastrointestinal tract, must be considered as only one manifestation of a general psychoneurotic disturbance. Its emotional background is similar to that of the neurotic disturbances of eating, and the therapeutic approach is the same. The symptom itself, and to be sure not the neurotic disturbance of the total personality, often can be combated by suggestion or hypnosis, persuasion, rest cures and sedative medication.[38] Since these do not get at the cause, they can be recommended only when the chronic vomiting is so stubborn that immediate help is indicated. The elimination of the symptoms alone, however, does not mean a cure of the neurosis itself, which after the vomiting is eliminated may show itself in less conspicuous but equally significant symptoms or in abnormal behavior in life.

DISTURBANCES OF THE SWALLOWING ACT

(Esophageal Neuroses)

Whereas in anorexia and in more specific eating difficulties the eating act itself is inhibited and in nervous vomiting the already incorporated food cannot be retained, in esophageal neuroses the act of swallowing is disturbed. The patient chokes on the food and cannot get it down. In many cases psychogenic cardiospasm is the physiologic basis of the symptom.[40] In other cases a subjective sensation of a foreign body, usually in the upper part of the esophagus, appears independent of eating (globus hystericus).

Kronfeld,[21] who subjected a series of patients with esophageal neuroses to systematic psychiatric study, distinguished two forms, a sensory hyperalgetic and a reflectory spastic. The sensory hyperalgetic form is often syperimposed on a local disturbance, whereas this association is not observed in the spastic form. The emotional basis of the symptoms is an unconscious rejection of incorporation, which is the result of aggressive impulses, often of a sexual nature (castration wishes), connected with eating and swallowing. Kronfeld tried to differentiate between the emotional background of anorexia, of esophageal neuroses and of hysterical vomiting. He compared the esophageal neurotic with the gambler: Both dare to put things in the mouth and expose themselves to an imagined danger. Whereas in the presence of anorexia the patient simply refuses to eat, in hysterical vomiting the conscious reaction comes only after the unconscious crime, symbolized by eating, has already been committed. Kronfeld found that disgust plays a very important role in this disturbance. According to him, disgust is a combination of temptation and rejection and shows an ambivalent attitude toward incorporation. Kronfeld's observations still have to be corroborated, although they are in close accord with general psychologic data on the eating and swallowing act.

A well defined disturbance of the swallowing function is known as cardiospasm—a term introduced by von Mikulicz in the nineteenth century. It consists in the contraction of the lower end of the esophagus and leads to a dilatation of the proximal portion. Recently Edward Weiss[36] subjected 9 patients to psychosomatic study. He called cardiospasm a psychosomatic disorder and differentiated somatic predisposition and emotional factors in its etiology. Superficially, according to him, the condition belongs to the group of conversion hysterias and as such expresses an unconscious symbolic meaning which can be stated as: "I cannot swallow the situation." It appears when a patient finds himself in an emotional impasse in regard to his external situation. In a deeper layer, sexual, hostile and selfpunitive trends are of etiologic significance. Weiss recommended a combined approach, mechanical dilatation and psychotherapy, and warned against neglecting the emotional factors. In one case, for example, the dilatation treatment was immediately followed by depression.

Therapy.—Kronfeld emphasized, in severe esophageal neuroses, the need for quick relief, and therefore he recommended any method which dispels the symptom, such as spasmolytic medication, diathermy and quickly effective forms of psychotherapy. Of course, here, as in other disorders, even after the symptom is broken the psychoanalytic approach is indicated, in order to attack the deeper emotional disturbances of the total personality, of which the esophageal symptom is only one manifestation.

DISTURBANCES OF THE DIGESTIVE FUNCTIONS

(Stomach Neuroses and Peptic Ulcers)

Stomach Neuroses.—Stomach neuroses display an enormous variety of polymorphous, ever-changing symptoms based on disturbances of the secretory and the motor functions of the stomach and the duodenum. It is extremely difficult to differentiate between neurogenic (central) and organic (local) disturbances. Many functional stomach symptoms are secondary results of faulty habits of eating. Of course such faulty habits as incomplete mastication and fast eating, air swallowing, immoderation and unwise selection of food are mostly the expression of emotional tendencies, and therefore in the last analysis these disturbances also can be considered as psychogenic.

Fundamentally, the over-taxation of the stomach by unhealthy eating habits may lead sometimes to local disturbance of the stomach (gastritis). These combined with the functional disturbances of nervous origin are responsible for the extreme variety and complexity of symptoms, which makes rigid differentiation between psychogenic (functional) and local (organic) impossible. The nervous disturbances of the stomach which manifest themselves may range from slight distress after eating, heartburn, loss of appetite, regurgitation or eructation of gas to severe gastralgia and severe and intractable vomiting. The physiologic basis of these different symptoms is just as varied as the symptoms themselves: Hypoperistalsis and hyperperistalsis, stenosis of the pylorus and hypersecretion or hyposecretion of hydrochloric acid. Recently Wolf and Wolff[43] confirmed the clinical findings made in the Chicago Psychoanalytical Institute[2] by observations on a patient having a permanent gastric fistula. They observed hyperemia, hypermotility and hypersecretion as an expression of hostile, aggressive feelings when the patient was inhibited, and noticed a return to normal when the patient regained his emotional security. Although these authors considered primarily the conscious mental content and therefore could not reconstruct in detail the psychodynamic situations, the relation between a longing for security and hyperactivity of the gastric functions can be clearly seen in their observations. Hypoacidity seems to appear most often in connection with depressive states and often appears in connection with fatigue. Chronic hyperacidity with its concomitant symptoms, again, has been often observed to have a psychologic background similar to that of peptic ulcer. However, in all patients suffering from psychogenic gastric disturbances, the repressed possessive, receptive, help-seeking, dependent tendencies play a predominant role. A strong fixation to the early dependent situation of infancy is always present. This is in conflict with the adult ego, hurts its pride, wish for independence and self-assertion and thus becomes repressed.[2] This conflict is most conspicuously present in cases of peptic ulcer (*vide infra*).

Therapy.—That all the great variety of functional gastric symptoms are influenced by worries, fear, family quarrels and business reverses belongs to the common knowledge of general practice. Continuous over-exertion and exposure to danger are other causative factors, as the extensive experiences of the war have shown most convincingly. The common denominator in all these emotional tensions is the creation of an intense longing for rest, security and help. Accordingly, the improvement of nervous stomach symptoms can be most successfully obtained by rest, change of environment and relief of emotionally disturbing life situations. The symptoms resist all forms of drug therapy while the patient is exposed to the stresses of everyday life. The same patient when on vacation or in a sanatorium shows quick recovery and is able to dispense with all dietary restrictions without any ill effect. Nevertheless, rest cures or changes of life situations must be considered only symptomatic therapy, because the underlying pathogenic emotional background is not removed. Most patients have to continue their present life and cannot remain permanently segregated and discontinue their work and family life; therefore, systematic psychotherapy directed toward the fundamental problems of the total personality is indicated for all serious involvements. The stomach symptoms must be considered only the indicators of an underlying personality disturbance. This point was impressively expounded by Menninger.[24] Undue attention given to these symptoms only supports the neurotic patient's evasion of those emotional problems which underlie the symptoms and thus contributes to the perpetuation of the trouble. The physician's obligation in such cases is to call the patient's attention to the secondary nature of his physical symptoms and to counteract his flight into organic sickness by urging him to a final show-down—that is to say, to undergoing psychotherapy, in which he may finally settle his emotional problems.

Peptic Ulcers.—Lately the significance of emotional factors in the causation of peptic ulcers has been more and more emphasized. But the more recent studies are only systematic confirmations of the isolated observations of a large number of clinicians who for long have suspected the importance of psychogenic factors. Von Bergmann[35] and Westphal[37] came to the conclusion that most peptic ulcers may be considered as the least unpleasant complication of functional stomach neurosis of long standing.

That a functional disturbance of an organ may in time lead to structural (organic) tissue changes is an etiologic fact of primary importance, which might be the solution for many etiologic riddles of modern medicine. I have discussed this problem in another place:[1]

> In these cases the pathological anatomical changes are the secondary results of disturbed function and the disturbed function itself is the result of chronic emotional conflicts. If formerly every pathological function was explained as the result of the pathological structure now another casual sequence has been clearly recognized: pathological function as the cause of pathological structure. Although this etiological view is not entirely novel—yet if so explicitly formulated, many clinicians who are raised in the tradition of Virchow's principle and are still under the influence

of the simple and experimentally validated etiological discoveries of bacteriology, are not inclined to accept it without reservation. Usually whenever a functional disorder is described it is accepted with some doubt and the hope is expressed that further more precise histological studies will finally disclose tissue changes. The modern clinician is inclined to fall back upon the well proved classical concept that disturbed function is the result of a changed morphological substratum.

Previously the scientific credo in medicine was that further finer histological studies will reveal an anatomical basis of all so-called functional disturbances; today we feel without questioning the soundness of this principle that in many cases a thorough investigation in the life history might reveal the functional beginnings of truly organic disturbances. In these early phases the disturbance of function has not produced as yet necessarily histologically discernible organic changes. The resistance against this concept is based on the erroneous dogma that disturbed function is always the result of disturbed structure and on the disregard of the opposite causal sequence.

At present it is difficult to foresee what types of organic diseases follow this etiological scheme. It is most probable that in the great chapter of medicine which might be called "Disorders of Unknown Origin," many will fall under this category.

Recently Taylor[34] found with the Wolf-Schindler gastroscope that peptic ulcers may develop in a stomach which is already the seat of diffuse hyperplastic changes in the mucosa (hyperplastic gastritis). My opinion is, however, that these hyperplastic changes probably are themselves the results of a functional disturbance (hyperacidity) of long duration. The etiologic problem is, then, to establish the origin of the chronic functional disturbances, and here is where the significance of the emotional factors become obvious.

Different authors found that certain types of person are more inclined than others to peptic ulcers. Alvarez[5] spoke of the efficient, active Jewish business man, the go-getter type, as being particularly disposed to peptic ulcers. Hartman[19] characterized as the peptic ulcer type the man who is "encountering obstacles that prove to him a trial and handicap, which he must, because of his nature, endeavor to overcome." He claimed that the Indians of Latin America and the Chinese coolies never have ulcers, and explained this as the result of the stoic, almost apathetic attitude, the lack of strain and ambition, characteristic of these races. According to him, ulcer is a disease of the civilized world and afflicts chiefly the striving and ambitious men of western civilization. Draper and Touraine[13] found typical of their patients a rejection of unconscious female tendencies, the same tendencies which, according to psychoanalytic study, it is preferable to describe as oral-receptive or oral-aggressive impulses, which are closely related to striving commonly regarded as female. The authors complemented their studies with anthropologic measurements and tried to describe the peptic ulcer type psychologically as characterized by the presence of masculine protest and rejection of female tendencies and anatomically as the asthenic or longitudinal type.

On the basis of studies carried out in the Chicago Institute for Psychoanalysis,[2] it could be assumed that gastric symptoms or even peptic ulcers may more frequently develop in one personality type than in others, but the exceptions which we have encountered at a very early stage of our research do not encourage us to expect such a simple and generally valid result. What we find characteristic is not so much a certain personality type as a typical conflict situation, which may develop in many very different personalities. This typical conflict is between the wish to remain in the dependent infantile situation, to be loved and cared for, and the pride and aspiration of an adult ego for independence, accomplishment and self-sufficiency. The two conflicting tendencies reinforce each other in a characteristic way. Many peptic ulcer patients show in their overt behavior the aggressive, ambitious, independent attitude in an exaggerated manner. They do not like to accept help and seek to burden themselves with all kinds of responsibilities. One often finds this type among efficient business executives. Deep in the unconscious is seen, then, the reaction to this extreme independence, as if the person were tired from all the responsibilities and struggles of his active life. In the depth of his personality his unconscious longing for the sheltered existence of the little child increases. He carefully hides this dependent attitude from himself, represses it, and thus it cannot find expression in overt behavior in life and personal relations. This repressed longing for love is the unconscious psychologic factor directly connected with the organic processes leading in the end to ulceration and explains why often rest cures, during which the patient is removed from the continuous responsibilities and daily struggle, are therapeutically so effective. After the symptoms become severe or threatening, or after an acute hemorrhage, the patient can give in openly to his tendency to flight from his responsibilities and does not need to repress it so severely. The severe organic symptoms justify the withdrawal.

A Psychogenic Theory of Ulcer Formation.—Early in this Chapter (*vide supra*, p. 826) the close association between the functions of nutrition and the wish for security, for help and for receiving love is mentioned. The infantile wish to receive, to be taken care of, to be loved, to be dependent on someone else, is most ideally gratified in the parasitic situation of the suckling infant. Thus these emotional qualities of receptivity, the wish to be loved and taken care of, become closely associated in an early period of life with the physiologic functions of nutrition. Being fed thus becomes the primordial symbol of being loved.

If the intense wish to receive, to be loved, to depend on others is rejected by the adult ego and consequently cannot find gratification in normal life relations, then only the regressive pathway remains open; the wish to be loved becomes converted into the wish to be fed. The repressed longing to receive love and help mobilizes the innervations of the stomach, which have been, since the beginning of the extrauterine life, closely associated with the most primitive form of receiving something, namely, with the process of receiving food. These innervations serve as a chronic stimulus of the stomach functions and lead to its dysfunction, since this stimulus of the stomach is independent of the normal organically conditioned stimulus, namely, the need for food; this stimulus has its origin in emotional conflicts entirely independent of the physiologic state of hunger. Persons who on account of the described conflict situation have to repress and abnegate their over-strong receptive cravings express them in the tacit physiologic language of the stomach functions. The stomach behaves all the time as if it were taking or about to take in food. The greater the rejection of every receptive gratification in life, the greater will be this unconscious wish (it may now justifiedly be called *hunger*) for receiving love and help. The patient wants food not because of organic hunger, but as a symbol of love and help.

My present notion is that the stomach under this permanent chronic stimulation behaves constantly as it does during digestion. A chronic hypermotility and hypersecretion may be the consequences. The empty stomach is thus constantly exposed to the same physiologic stimuli to which under normal conditions it is exposed only periodically, when it contains or is about to receive food. The symptoms of nervous stomach, epigastric distress, heartburn and belching probably are the manifestations of this chronic stimulation, which sometimes may even lead to ulcer formation.[2a]

The question whether a constitutional or an acquired weakness of the stomach is responsible for the fact that only in certain cases of gastric neurosis or chronic functional hyperacidity do real ulcers develop must be left unanswered at present. There is a growing mass of experimental and clinical evidence of the validity of the theory. Among internists, Alvarez considers the chronic stimulation of the empty stomach one of the etiologic factors of peptic ulcer. Interesting in this respect are the experiments of Silbermann[32] with sham feeding of dogs. An artificial fistula is introduced, and the food which the dog swallows falls to the floor; the dog snaps it up again, repeating this procedure often for as long as three-quarters of an hour. Such powerful stimulation of the gastric secretion of the empty stomach, according to that author, regularly leads to ulcer formation. The peptic ulcer patient's condition is in many respects similar: His stomach is in a state of chronic stimulation, not as a result of eating but of repressed psychologic drives to be loved, to receive or to take aggressively what he does not get freely. These tendencies are repressed and thus excluded from normal outlet through voluntary behavior. They discharge themselves through the vegetative system. The wish to be loved, closely connected with the wish to be fed, stimulates, through the parasympathetic pathways, the stomach functions. Recently Schmidt and Fogelson[30] repeated Silbermann's experiments and could not corroborate his findings. On the other hand, experimental studies[20] corroborate the assumption that one causative factor in ulcer formation may be continuous secretion under the influence of chronic psychologic stimuli. The maximum permanent secretion in the stomach occurs during the night in cases of stomach disease, in the great majority cases of duodenal ulcer. They found high nocturnal secretion also in cases of chronic gastritis and of "vegetative neurosis" with a healthy stomach. Also, Winkelstein observed high acidity in ulcer patients as a reaction to sham (psychic) feeding. He observed higher nocturnal acidity in cases of gastric or duodenal ulcer than in control cases. All these observations show that the peptic ulcer patient's stomach is particularly sensitive to nervous stimuli and that continuous secretion is common. It seems, therefore, that the significant point is not the absolute grade of acidity but the chronic state of excitation of the stomach, the chronic secretion of gastric juice.

This chronic excitation of the stomach by emotional tension is not limited to the secretory function alone. The motor functions of the stomach also are probably involved. The specific significance of these factors for ulcer formation is, however, not yet clarified. Spasm of the pylorus causing prolonged retention of acid gastric content is a possible etiologic factor. Also, the blood supply of the stomach might well be influenced. Necheles,[27] in fact, following Dale and Feldberg's[12] work, found that acetylcholine, which under parasympathetic stimuli is liberated in the stomach wall, causes anoxemia in the tissue. Acetylcholine has an influence also on the acid secretion. Necheles confirmed also Winkelstein's findings concerning the higher than normal parasympathetic irritability of ulcer patients.

Therapy.—Since as a result of preceding neurotic conflicts a serious local organic condition has developed, the first therapeutic concern is the local condition itself. Psychotherapy is mainly of preventive value. In most cases, before active ulcer develops there is a longer or briefer period of functional symptoms, when thorough psychotherapy is indicated. Chronic hyperacidity and other stomach symptoms are the first warning signal that the nervous control of the stomach functions is disturbed. In the presence of these, concentration on the local symptoms and neglect of the personality factors is a great error.

Since peptic ulcer is chronic, psychotherapy, together with the medical care of the local condition, is indicated even after the active ulcer has developed. According to our systematic studies at the Chicago Institute for Psychoanalysis, peptic ulcers often develop in personalities with a deep-seated neurotic conflict.[2] Therefore, psychoanalytic treatment offers the best approach to the fundamental emotional factors. According to accumulated experiences of recent years, in certain cases psychoanalytically oriented psychotherapy of short duration can be successfully applied.

DISTURBANCES OF THE ELIMINATIVE FUNCTIONS

Psychology of the Excremental Functions.—After eating, the excremental functions play the most important role in the emotional life of the infant. Like eating, the excremental functions become associated with certain typical emotional attitudes in early life. The psychologic aspects of these functions were wholly unknown or neglected before the advent of psychoanalysis. These matters were among those excluded from the parlors as well as from scientific investigation and even from medical consideration. There is a tremendous psychoanalytic literature on this subject, covering data carefully observed for thirty years.[17] I shall sketch only the most fundamental facts.

While the wish to receive or to take by force what is not freely given, to be loved, to lean on someone, and the urge for security are most closely associated with the incorporative function of eating, the eliminative act becomes connected in early life with the emotions of possessiveness, pride in accomplishment and the tendency to give. Also, certain types of hostile impulses—to attack, to soil, to disparage—are connected with these functions.

The pleasure sensations connected with suckling are soon thwarted in early life. To weaning from the nipple the child reacts with thumb sucking, which, however, is soon checked by the adult. Soon the child discovers that a similar pleasure sensation can be procured at the other end of the alimentary tract by the retention of the feces. Here also a solid body irritates a mucous tubular organ. This type of pleasure is more difficult for the adult to interfere with. The sense of independence from the interfering world around, therefore, soon becomes connected with the excremental act. The child soon loses his sovereignity over his excremental functions during training to cleanliness, when adults try to influence the child to engage in his excremental functions at regular intervals, which means for the child compliance with the adult's wishes. The child is often urged to part from his excrement not when he wishes but when the adults consider it appropriate, and receives in exchange praise, love and sometimes even some material goods, such as a piece of candy. Thus the excrement becomes first associated with the concept of possession, and its close relation to money, one of the best established facts of psychoanalysis, can be explained easily on this basis. Every excremental act the child can evaluate as a kind of donation to the adults, which is often reinforced by many mothers' great interest in their children's excrements. (The German expression for the bowel movement of the child, *Bescherung,* means gift.)

In the early period the child's attitude toward excrement is coprophilic. The excrement is a valuable possession, a source of pleasure and something which can be exchanged for other goods. This coprophilic attitude, however, soon is broken by educational procedures and changed into its opposite, disgust and depreciation. This becomes, then, the basis of the sadistic aggression-and-soiling connotation of the excremental act. The excrement becomes then a soiling weapon, and the act itself has assumed a deprecatory significance. This can be observed most clearly in the little street urchin who defiantly shows his hindparts and often accompanies this gesture with some kind of aggressive invitation. All these emotional connections, of course, more or less disappear in later life from the conscious personality, but they remain deeply rooted in the emotional life and often appear in the neurotic symptoms of mentally disturbed patients and even in the dreams of normal adults.

These few facts of emotional development may give some idea of how and why the excremental function becomes connected with the feeling of accomplishment, of giving or of attacking, soiling and depreciating and also of why the excrement becomes the first symbol of possession. For the understanding of the psychologic background of disturbances of the excremental functions, both psychogenic diarrhea and constipation, the knowledge of this emotional development is of fundamental significance.

Chronic Diarrhea, Spastic Colitis, Mucous Colitis, Ulcerative Colitis.—It is an open question whether these different forms of intestinal disturbance are different phases or manifestations of the same basic condition, with chronic diarrhea and spastic colitis, which may in many cases develop into the mucous and ulcerative forms, as the functional phase. There is no doubt, however, that emotional factors have an influence on all. How much this influence is an aggravation of an underlying local disturbance and how much the emotional factors are themselves of etiologic significance is not clear.

Since chronic diarrhea can be a symptom of both organic and neurotic disturbances which may be present simultaneously, it is not always possible to distinguish clearly the role of neurogenic or local pathologic factors. Simple chronic diarrhea is often the bodily expression of a psychoneurotic condition, and in certain cases it is the central symptom. Daily evacuation of small or large quantities of liquid stool may take place more or less frequently with or without tenesmus: In some cases 20 to 30 evacuations may be observed in one day. Usually there are no organic findings whatever. Many patients react to the diarrhea with worry and anxiety—they are fearfully expecting it, and their concern about it often becomes a central issue of their daily life. Patients often can retrace the precipitating factors to dietary transgressions, but most patients can discover a connection with emotional tension.

Mucous colitis for long has been considered a neurosis. Recently White, Cobb and Jones[37] came to the conclusion that mucous colitis is a physiologic condition of the colon brought about through the action of the parasympathetic nervous system, and that the parasympathetic over-stimulation is in a great majority of cases (in their series 92 per cent) the result of emotional tension. They described certain personality trends which seem to be characteristic. Their psychologic findings coincided to a great extent with those of the Chicago Institute for Psychoanalysis on different forms of colitis.[39] Over-conscientiousness, dependence, sensitivity, anxiety, guilt and resentment are the emotional tensions most commonly found in patients suffering from mucous colitis. Many authors are inclined to believe that even an ulcerative colitis ultimately may develop on a nervous basis.

Murray,[25] in 12 cases of ulcerative colitis, found that emotional conflicts were precipitating factors at the onset of the symptoms. The conflicts usually concerned marital relations. Bell[6] described in detail the emotional background of a woman with colitis. Marital conflicts were in the foreground, and the guilt feeling toward the divorced husband dominated the picture. Sullivan and Chandler[33] could relate to emotional difficulties the outbreak and course of ulcerative colitis in 6 cases. Wittkower,[42] in 40 cases of ulcerative colitis, found a preponderance of neurotic trends and emotional factors precipitating the onset of the symptoms.

The psychoanalytic study of patients suffering from chronic diarrhea and spastic and mucous colitis shows a typical conflict about their strong demanding (oral-aggressive) and receptive wishes: They wish to compensate for these dependent wishes by activity, substituting attacks of diarrhea for real activity and accomplishment.

Another unconscious emotional factor connected with diarrhea is the desire to give compensation for all those things which the patient wants to take away or receive. This appears often as worry about certain duties and obligations, to give money or support others, to make strenuous efforts and to work. The patient often, therefore, is described as over-conscientious. At the same time, however, he has a violent reluctance to exert himself, to engage in systematic strenuous work and to fulfil those obligations to which emotionally he feels compelled. The repressed psychologic factor which can be brought into connection with the symptoms is here the strong tendency to give, to make restitution. Often the patient becomes dependent on others, but feels that he should do something to give compensation for all that he receives. But instead of real accomplishment he satisfies his conscience with this infantile form of gift—that is to say, the intestinal content.

In this respect the patient shows a conspicuous difference from the peptic ulcer patient, who also over-compensates his passive and receptive tendencies. The peptic ulcer patient does this, however, by real exertions, work, efficiency and aggressive, independent behavior in life. The diarrhea patient over-compensates for passivity only by the unconscious symbolism of the excremental act, an emotional substitute for performance, accomplishment, work, gifts and obligations toward others. The physiologic basis of such emotionally conditioned chronic diarrhea is obviously the chronic excitation of the peristaltic bowel activity conducted to the intestines through parasympathetic pathways. The described emotional tendencies to give and to accomplish, which arise as compensation for strong receptive or taking tendencies, if repressed and thus excluded from voluntary expression, seem to have a specific influence on the bowel functions.[4]

Hostile impulses also enter the picture and contribute to development of guilt feelings and the wish to give restitution. They may also have a direct effect on the intestinal symptoms.

It is only natural that in women the conflict about giving and receiving often centers around pregnancy. Giving birth to a child is obviously the most creative function of the female organism. The patient rejects pregnancy, and the diarrhea serves as a substitute for the dreaded act of giving birth.[26]

In a recent publication Brown, Preu and Sullivan[9] reported results in 30 psychiatrically studied cases which were quite in accordance with my analytic findings on spastic and mucous colitis. Also, they found characteristic of these colitis patients a lack of output of drive and the tendency to give up in the face of difficulties and to avoid responsibilities.

I observed these emotional features with unusual clarity in a case of chronic diarrhea:

A patient, aged forty-eight years, was suffering from a chronic severe diarrhea. This condition with some remissions had lasted over eight or nine years. At the beginning of the condition some mucus was found. Later the patient had several watery stools during the day, felt fatigued and was extremely concerned with his bowel movements. Every day he dreaded his diarrhea, which was not connected with any pain, and anticipated it fearfully. After evacuation he felt exhausted, unable to work and concentrate. He seldom could engage in continuous business activity and had to take frequent vacations, during which his condition was improved considerably. He lived on a strict diet, avoiding alcoholic drinks, roughage, fats and all heavy meals. The various drugs he tried remained ineffective. Like many colitis patients, he reacted favorably to psychoanalytic treatment shortly after its beginning, and his diarrhea almost immediately disappeared and returned only very occasionally. It was obvious that the emotional relief which the treatment gave him was of immediate symptomatic benefit. The mental picture revealed during the treatment was a typical one of conflict between a strong sense of obligation toward his family and others and a strong passive, dependent attitude.

The patient had married into a wealthy family, which was obviously the main factor disturbing his emotional equilibrium. The wife's family, although not directly, made him feel that he was an intruder, but at the same time made it possible for the couple to live according to the standards to which the wife was accustomed. They also helped him develop his business and assisted the patient's firm financially. From the time of his marriage the patient's life consisted in a desperate struggle to make good by his own effort. He pursued his business activities with a hetic energy and at the same time internally revolted against all these exertions, wanting to live a leisurely life consisting of travel, exercise and the reading of fine books—the life of a gentleman. The analytic session brought out with utmost clarity this conflict, which was not fully conscious and verbalized before. The patient reacted with diarrhea whenever the urge for accomplishment, work and fulfilling certain obligations became very intense in him, but at the same time the resistance to carrying out these things in reality also became equally potent. It seems that for this conflict the diarrhea was an infantile method of solution. *For his unconscious mind* bowel movements still meant accomplishment and giving. That explains why after every evacuation he emphasized the feeling that he was totally cleaned out and exhausted. The bowel movements substituted for real exertion in life and gave him also an excuse for relaxation and being taken care of.

The most interesting part of this case is that about eleven years before the diarrhea developed the patient was operated on for gastric ulcer. The ulcer symptoms started when he was a student and made strenuous efforts to forge ahead under the influence of an ambitious mother. The patient fully concentrated on making a career. After the ulcer symptoms had lasted for five years the patient was operated on for perforated ulcer. At this period of his life he was extremely active and concentrated doggedly on his studies. The diarrhea, which started eleven years later, developed after marriage, through which he became wealthy and to some degree dependent on his wife's family.

This case demonstrates most clearly the fact that it is erroneous to assume that certain psychogenic disturbances develop only in certain personality types. The organic condition can be clearly correlated to certain psychodynamic situations but not to permanent personality types. It is obvious that here the same personality was exposed to different conflict situations: While a student he worked hard and reacted to that with a strong longing for dependence, which he did not admit to himself. At that time a peptic ulcer developed. When living in affluence but in emotional dependence on the wealthy family of his wife, a strong sense of obligation—to work hard—developed. At this time chronic diarrhea appeared. His diarrhea was a means of relieving this sense of obligation by a primitive form of giving and accomplishment.

Therapy.—Although dietary therapeutic measures may be of benefit, the primary concern must be directed toward the emotional disturbance itself. Here, as with all organic neuroses, rest cures and sedative medication may alleviate symptoms, but the basic condition can be approached only by psychotherapy.

In cases of *chronic diarrhea, spastic and mucous colitis,* the value of the psychotherapeutic approach has been clearly demonstrated by the systematic studies of the Chicago Institute for Psychoanalysis. Our experience is that after successfully concluded psychoanalytic therapy most patients can dispense with any further dietary regulation and medication. Of course, for all types of disturbance there are refractory examples which cannot be successfully or permanently influenced by either organic or psychotherapeutic methods. Successful treatment of ulcerative colitis by psychotherapeutic methods has been reported.[43]

Chronic Psychogenic Constipation.—This condition must be distinguished from the constipation observed in spastic colitis. In some cases constipation is the only gastrointestinal symptom. Although constipation may be a manifestation of various organic conditions, in general chronic constipation is purely psychogenic. The psychologic findings in cases of chronic constipation are typical and constant. A pessimistic, defeatist attitude—a distrust or lack of confidence regarding depending on others, the idea of being rejected and not loved—can often be found in these patients. In an exaggerated form this attitude is found in paranoia as well as severe melancholia. Chronically constipated patients have a trace of both attitudes: the distrust of paranoia and the pessimism and defeatism of melancholia. In this respect the statistical studies of Menninger and me[3] are of interest. We found that a large majority of patients suffering from persecutory delusions are severely constipated. Also, as is well known, melancholic patients show a conspicuous inclination toward constipation.

The emotional undertone of psychogenic chronic constipation could be verbalized as follows: "I cannot expect anything from anybody, and therefore I do not need to give in anything. I must hold on to what I have." This possessive attitude, which is the outcome of the feeling of rejection and distrust, manifests itself then organically in the constipation. The excrement is retained as if it were a valuable possession, in accordance with the early coprophilic attitude of the child. Another psychologic finding—usually less on the surface, more repressed—is an unconscious aggressive depreciatory and hostile attitude against others, which may be the reaction to the general feeling of being rejected. This hostile aggressive depreciatory soiling attitude is deeply repressed and inhibited, and the inhibition extends over the excretory function, which for the unconscious life has the significance of hostile attack and soiling.[44]

Therapy.—Chronic constipation is considered a trivial symptom, and in most cases a symptomatic approach, by dietary measures, laxative medication, enemas or massage, suffices for all practical purposes. On the other hand, this symptom may be the manifestation of a deeper-seated emotional disturbance, and psychoanalysis, as well as briefer psychotherapeutic procedures aiming at the uncovering of unconscious conflicts, often shows excellent results. Long-standing constipation often responds favorably to the psychotherapeutic approach. Many patients who for years were accustomed to using purgatives have been able to dispense with all further use of drugs. Of course, constipation is only one, and often not even the most significant, manifestation of a disturbance of the patient's emotional outlook toward life and toward others, and therefore in suitable cases psychotherapy must be directed toward a reorientation of the total personality.

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CHAPTER XLIII

THE GENERAL TREATMENT OF PSYCHOSOMATIC DISTURBANCES OF THE GASTROINTESTINAL TRACT

THE effect of emotional stimuli on the gastrointestinal tract is a new field of study for gastroenterologists. In the preceding chapter, Alexander has exhaustively explored the psychodynamics and the psychogenesis of gastrointestinal syndromes. In other chapters, various contributors have alluded to the emotional aspects of their respective clinical pictures. Therefore, it is timely that some general medical management be outlined, not only for the relief of these symptoms but for putting the patient in a more nearly physiologic state to prevent disturbance of the harmonious environment of the gastrointestinal tract by untoward emotional stimuli.

Three basic considerations confront the physician in the treatment of patients so affected:

1. A dietary regimen should be so constructed as to take into account the irritability of the mucous lining of the gastrointestinal tract resulting from the pathologic condition; to prevent stimulation of reflex phenomena by various foods; to assure adequate vitamin and mineral intake, and to promote return of body metabolism to near normal.
2. If alterated emotional stimuli result from cortical influence on the midbrain, medication should be directed at the eradication or removal of their influence.
3. If stimuli reaching the gastrointestinal tract by way of the parasympathetic nervous system produce disturbance, therapy should be directed at the site of innervation of these nerves, to prevent the altered stimuli from producing these changes.

Diet.—First in importance in the therapeutic regimen is diet.[3] It has previously been reported that fatigue in emotionally disturbed patients may result from the hypoglycemia due to a presumed stimulation of the islands of Langerhans, leading to hyperinsulinism.

In a subsequent and more intensive study, to be reported, my associates and I observed a definite disturbance of carbohydrate metabolism in a large number of patients with fatigue. Furthermore, the postdigestive fatigue noticed was interpreted as an aggravation of increased stimulation of the islet cells due to the intake of free sugar in the diet. Because free sugar, given as such, is readily absorbed and readily excreted from the liver, its administration seems only to intensify a physiologic process that it is desirable to depress. Therefore, free sugar in the diet, in no matter what form, should be reduced as much as possible.

The diet should be high in protein, moderately high in fat (except in patients with outspoken abnormality of the gallbladder and those having hyperkinetic dyskinesia of the gallbladder) and relatively high in carbohydrates. The carbohydrates are in a more complex form than when free sugar is given and take a longer period for complete digestion. Two observations establish this: 1. The slow injection of dextrose in normal dogs greatly increases the tolerance of these animals to subsequent more rapid injection. 2. The deaminization of protein and the formation of carbohydrate go on at a much slower rate in the liver. Therefore, secretion of dextrose is prolonged, and the postdigestive hypoglycemia in these patients will be delayed, if necessary, to the next intake of food. As an additional factor of safety to prevent hypoglycemia from becoming manifest in these patients, we gave more frequent feedings than the normal three meals a day. Later we instituted a feeding before the patient retired, to prevent hypoglycemic manifestations between the last regular meal at night and the subsequent breakfast. This latest addition to the dietary regimen is one of the most important, in connection with the medication. Therefore, the patient received his three main meals, a midmorning feeding, one or two midafternoon feedings and a feeding before he retired at night.

Our experience leads me to believe that emotionally disturbed patients frequently have a disturbance of the pancreas in addition to other disease of the gastrointestinal tract.

The diets outlined in subsequent chapters are adequate and scientifically calibrated, except for the elimination of free sugar, discussed previously.

Medication.—The second consideration in treatment should be the elimination of the cortical influence. Of all the drugs that have been used, the barbiturates are the best, and in my experience phenobarbital is the simplest, most satisfactory and easiest to administer. It is well tolerated; few, if any, allergic manifestations ensue, and the patient experiences a great deal of relief both psychologically and symptomatically. It may be given in $\frac{1}{4}$ to 1 grain doses, four times a day, *e. g.*, after each meal and at bedtime. The last dose is important, to bring about a more nearly normal state of the brain during sleep. All dosages depend on the therapeutic needs. For patients who are vomiting, hypodermic administration may be practiced temporarily.

The use of paralyzing drugs to prevent stimuli at the site of innervation from reaching the affected organ is the final general consideration. Many drugs, *e. g.*, atropine, novatropine, syntropan, transentin and others, have been used. I believe atropine is the drug of choice, giving generally satisfactory results. Doses as high as 1/75 grain three times a day have been tolerated, without untoward results. Unusual dryness and visual disturbance are frequently met, but unless they are too distressing, they should be disregarded. If, however, they form an important objection, syntropan may be substituted, in a dose of 50 to 100 mg. three times a day. One might raise the question of cardiac disturbance resulting from the use of atropine, but in elderly patients or those with myocardial or valvular lesions, the atropine has been cautiously prescribed, and the dosage well calculated to prevent untoward results. In a group of patients so treated, no unfavorable cardiac manifestations have occurred.

With this treatment also, as with dietary and barbiturate management, a small dose of atropine (*e. g.*, 1/175 to 1/200 grain) is given the patient on retiring. Even if emotional stimuli are presumably attacked at the source, some get through to the parasympathetic nervous system and have their stimulatory and depressing effects. Therefore, this night dose is important, to take care of the prolonged period of sleep. In addition, small doses of thiamin chloride are given three times a day with meals (never at bedtime) in order to assure more complete utilization of dextrose in the muscle metabolism.

Conclusion.—In my experience, these general measures, combined with the symptom management described elsewhere in this volume, form a simple, direct and satisfactory method for handling gastrointestinal disturbances of psychosomatic origin. Further exploration of this field, with adequate scientific controls, should yield additional measures for the relief of such physiologic disturbances, which constitute the major portion of gastrointestinal disorders.

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CHAPTER XLIV

ALLERGY OF THE GASTROINTESTINAL TRACT

Definition.—Gastrointestinal allergy is not an easily recognizable disease entity nor yet a well delimited syndrome. It is marked by functional and structural disturbances of the gastrointestinal tract of allergic origin. Allergic phenomena are generally variable, temporary and reversible, and the gastrointestinal tract throughout its whole length is vulnerable to them. There is a varying group of symptoms which either mimic those of well defined clinical gastrointestinal syndromes or are so bizarre, vague and variable that they defy classification.

In this anomalous situation, wherein a single constitutional factor, allergy, may simulate many etiologic agents, it is obvious that clarity can be maintained only by fastening on those phenomena which experience has shown to be characteristic of allergy and to pursue them in the light of this experience step by step and eventually to arrange them into a concept which will make possible their differentiation from those due to other causes. The difficulties in this method are manifest. To the spasm, edema, flushing, increased secretion of mucus and eosinophilic cellular infiltration characteristic of allergy the gastrointestinal tract can only respond by anorexia, vomiting, pain, diarrhea or the like. Proof that these are due to allergy must be chiefly indirect, and judgment must be leavened with the knowledge that allergic persons are subject to the same gastrointestinal ailments as nonallergic persons. The proof that certain gastrointestinal symptoms are the result of allergy generally rests on the evidence that in allergic persons those measures which give relief from known allergic disturbances give relief from accompanying gastrointestinal disturbances, and those measures which reproduce known allergic disturbances reproduce the accompanying gastrointestinal disturbances.

Other objective signs characteristic of allergy in the organs of that tract are still essentially lacking. However, the fact that gastrointestinal allergy rarely if ever occurs without objective evidence of allergy in other systems of the body may be used as an aid in diagnosis. The recognition or the identification of the allergic person may thus become the first necessity in the recognition and differentiation of gastrointestinal allergy.

ETIOLOGY

The incidence of allergic disease in general has been fairly well established through the surveys of Cooke,[7] Piness and Miller[18] and more recently of Service,[25] who estimated that 3.5 to 5 per cent of the general population are affected. Balyeat expressed the belief that this figure should be nearer 10 per cent. The exact incidence of the gastrointestinal types has not been determined, but it is agreed that they are more common than is generally recognized.

Rowe[20] reported a predominance of females over males in his study of 100 cases of gastrointestinal food allergy. Other observers have not corroborated these findings. That there is a definite preponderance of females over males in the mucous colitis group appears to be true. In the group presenting symptoms simulating gastric and duodenal ulcer, however, males seem to predominate.

Age apparently has no influence on allergy. It may and does occur from infancy through adult life, but the symptoms are influenced by the age factor, as will be observed by a study of the individual types. The generalization that gastrointestinal allergy occurs most commonly in the first decade of life is still open to question.

A positive history of hereditary allergy is often a valuable clue in establishing the identity of the allergic person. Most authorities believe that the allergic constitution is hereditarily transmitted, and in practice one finds that approximately 50 per cent of allergic persons give a history of allergy in immediate forebears and siblings.

IDENTIFICATION OF THE ALLERGIC PERSON

Turning next to the patient himself, a past or immediate history of such characteristically allergic symptoms as eczema, urticaria, hay fever and bronchial asthma are *prima facie* evidence of allergy. It is the recognition of less characteristic or obvious allergic symptoms that difficulties most frequently arise. Since one must rely chiefly on evidence available from the respiratory system to lead to the realization that the accompanying gastrointestinal symptoms are allergic, it is well here to emphasize the frequency with which allergic respiratory disturbances are mistakenly ascribed to infection.

In this class are many so-called colds, sinusitis, tonsillitis, bronchitis and even pneumonia. All have in common a recurrent and often an irritatingly persistent course and a tenacious refractoriness to traditional treatment. Dating back, as they often do, to childhood and even infancy, such symptoms are a valuable reminder of the allergic constitution on which they may be based.

Certain objective findings tend to confirm such suspicions as may have been aroused by the aforementioned hereditary history and clinical course. The mucous membranes of the nose, throat and eyes often show a typical allergic transformation, at times more or less modified by superimposed infection, but nevertheless recognizable either by direct observation or by histologic examination. Such evidence is proof that one is dealing with an allergic person.

Only two laboratory findings are helpful in identifying the allergic person: (1) blood eosinophilia, which must be differentiated from that produced by helminthic infestation, periarteritis nodosum or eosinophilic leukemia, and (2) eosinophilia of the nasal smear, which, if of sufficient degree, is pathognomonic of allergy. Skin tests with protein are not included as a laboratory aid in diagnosis, because it is unlikely that they will be resorted to until after the diagnosis is made or at least suspected, nor should they be used promiscuously or as a routine measure without some logical basis, such as that heretofore outlined. They should be reserved generally for discovering specific causes of symptoms in allergic disturbances and not used for the routine diagnosis of allergy.

Emphasis has been placed on the identification of the allergic constitution in patients presenting themselves because of gastrointestinal symptoms, not only because this is often the only inkling which may lead to recognition that such symptoms are allergic but because historically the frequent association of symptoms known to be allergic with gastrointestinal disturbances led to the creation of the concept of gastrointestinal allergy.

Other confirmatory evidence will be brought out in the discussion of the various gastrointestinal syndromes which have been shown to be related to allergy by experience, by their reproduction at will and by their relief by measures directed at their allergic cause.

Historically, two fallacies have arisen in the field of gastrointestinal allergy. The first would identify gastrointestinal allergy with food allergy, a fallacy which is controverted by the frequently repeated production of abdominal pain by injections of pollen antigen and the frequent occurrence of abdominal pain in persons sensitive only to inhalants. Duke[10] and others observed abdominal symptoms from pollen. Seasonal hay fever, in women particularly, is frequently complicated by mucous colitis. Children sensitive to inhalants, particularly to emanations from cat, dog, and horse, frequently have abdominal pain, edema of the lips, nausea and vomiting preceding their respiratory symptoms. Freeman[12] observed abdominal pain following injection of pollen antigen, while Black[3] and Pollia[19] reported gastric distress following oral administration of pollen antigen. The second fallacy associates gastrointestinal allergy chiefly with infancy and childhood; this has been denied by experience and is attributable only to the mistaken belief that food sensitivity occurs almost entirely in these age groups.

CLINICAL CLASSIFICATION OF GASTROINTESTINAL ALLERGY

Keeping in mind that the allergic process manifests itself in the tissues by spasm, edema, vasodilatation and cellular infiltration which may lead to hemorrhage, ulceration, smooth muscle hypertrophy and connective tissue thickening, one may anticipate, so far as the gastrointestinal tract is concerned, every degree of physiologic disturbance of which that tract is capable, from the vaguest indigestion or perianal itching to the most spectacular abdominal pain and dysentery. A classification of such symptoms into syndromes merely serves the purpose of emphasizing the importance of allergy in gastrointestinal diagnosis and of providing a frame of reference to aid in classifying a still obscure field of medicine.

Classification of Allergic Syndromes of the Gastrointestinal Tract

1. Anorexia (difficult feeding, malnutrition)
2. Persistent vomiting of infancy and childhood
3. Cyclic vomiting
4. Pyloric stenosis and pyloric spasm of infancy and childhood
5. Angioneurotic edema of the lips, face and tongue
6. Cankers of the mouth
7. Indigestion (dyspepsia simulating peptic ulcers or gallbladder disease, etc.)
8. Acute conditions within the abdomen; Henoch's purpura; allergic symptoms simulating acute intestinal obstruction, acute appendicitis, etc.
9. Chronic abdominal pain; allergic symptoms simulating chronic appendicitis, chronic intestinal obstruction, etc.
10. Mucous colitis; spastic colitis
11. Pruritus ani

Anorexia (Difficult Feeding, Malnutrition).—The infant or child classified by the pediatrician as a "feeding problem" is often an allergic child. All degrees of difficulty may be encountered, from mere dislike of particular foods to dislike of all foods, and from mild "stomach upsets" to persistent vomiting and marked malnutrition. In infancy, the association of abdominal pain and nausea with food dislikes is obviously undeterminable, but in older allergic children anorexia is often the result of actual abdominal pain and nausea after eating foods which the child often definitely states he dislikes. Such bouts of pain and nausea are often accompanied by an exacerbation of nasal obstruction and asthma and are relieved simultaneously with the relief of these respiratory symptoms.

Persistent Vomiting of Infancy and Childhood.—Persistent vomiting may occur within a few days to several weeks after birth and in its milder forms may continue until late childhood. Both breast-fed and artificially fed infants may be affected. Vomiting may come on immediately after feeding or at any time of the day or night, is often accompanied by evidence of abdominal pain and may, if continued over a long period, even though intermittent, produce varying degrees of malnutrition. An individual attack may so disturb the body metabolism as to initiate an episode of typical cyclic vomiting or be so persistent as to lead to operation for pyloric stenosis. Casparis[5] has reported 5 such cases in which operation showed no anatomic abnormality of the pylorus.

Food sensitivity is generally the cause of the symptoms in this group, and in bottle-fed infants milk is usually the specific offender. In the breast-fed infant any food may be the cause of symptoms, since it has been demonstrated that the unaltered protein in the mother's diet may be secreted with the breast milk. In older children it is often possible to confirm the diagnosis through respecting the child's food dislikes and thus alleviating the symptoms.

Cyclic Vomiting.—When nausea leads to vomiting and starvation, the well known vicious cycle of acidosis or alkalosis and vomiting may occur periodically, giving to the syndrome its appellation "cycle." It is hardly likely that all cyclic vomiting is due to gastrointestinal allergy, but it is not only conceivable but proved by actual experience that the nausea and vomiting of gastrointestinal allergy occurring periodically may institute the cycle.

Cyclic vomiting occurs generally in children past the age of two years, the interval between attacks varying from six days to several months. In allergic children seasonal types may be due to seasonal foods, but not infrequently the seasonal summer type may be due to pollen and the winter type to environmental inhalants, whether or not there is associated hay fever or asthma. The treatment of the immediate attack is that usual in pediatric practice. The prevention of future attacks is dependent on the recognition of the allergic background responsible for initiating the cycle.

Pyloric Stenosis and Pyloric Spasm of Infancy and Childhood.—As yet there is no satisfactory or generally acceptable explanation of the cause of these syndromes. Nor is there a clear dividing line between spasm and stenosis or definite information that spasm leads to stenosis or that they are two distinct conditions. The theory that both may be due to gastric allergy is based on two reports[6] of a positive family history of allergy in every case of pyloric stenosis investigated. Cohen and Breitbart theorized that the only essential difference between pyloric obstruction with hypertrophy and without hypertrophy may be due to the time at which sensitivity occurs and its duration. They classified the onset of sensitization as follows:

1. Active sensitization *in utero* early in prenatal life
2. Active sensitization *in utero* late in prenatal life
3. Active sensitization after birth from a sensitizing dose received *in utero*
4. Active sensitization after birth from a sensitizing dose received after birth
5. Passive sensitization *in utero*

Our own observations were made on a group of infants operated on for pyloric stenosis at the Los Angeles Children's Hospital. We found that some manifest type of clinical allergy later developed in 29 per cent, a much higher proportion than one would anticipate in a nonallergic group of children. We have found also, although the number of cases observed was small, that by the Prausnitz-Küstner indirect or passive transfer test reagins can frequently be demonstrated in infants with pyloric stenosis. It would, therefore, seem probable that pyloric stenosis is at times mediated by allergy.

Angioneurotic Edema of the Lips, Face and Tongue.—This syndrome generally appears first in infancy and usually occurs on the addition of some new food, most commonly egg, to the infant's diet. Immediately on ingestion of the offending food there occurs a spectacular urticarial swelling of the lips and tongue, which may spread to the whole face. There are violent vomiting and colic and often accompanying severe bronchial asthma and hay fever. Milder reactions may consist merely of a perioral erythema, sneezing, mild wheezing and colic, with more or less generalized urticaria. The immediate reaction is generally easily controlled by the hypodermic injection of 1:1,000 epinephrine, and recurrence is prevented by avoidance of offending foods.

Cankers of the Mouth.—Canker sores in the mouth may occur as a separate condition or (usually) in association with some other allergic disorder. They have an acute onset but a rather chronic course, recurring periodically, usually in the young and the middle-aged. The lesions are observed in the mucous membranes of the cheeks, lips, gums, palate, tongue and posterior pharyngeal wall and vary in size from that of a millet to that of a navy bean. They do not tend to coalesce and rarely occur singly, and the pain is severe out of proportion to the size of the lesion. Beecher[2] described their color as varying from grayish to yellow, resembling a false membrane. Those observed by us were grayish, surrounded by an inflammatory area, and the edges of the ulcers were sharp and regular. Later they may have an irregular edge. Skin reactions to food allergens occur frequently. Beecher reported 3 patients sensitive to foods, as were those observed by us in the group in which we were able to establish the cause.

Indigestion (Dyspepsia Simulating Peptic Ulcer or Gallbladder Disease).—Gastric allergy, dyspepsia or indigestion, is the most common form of gastrointestinal allergy. It occurs usually in adults and affects men preponderantly. The symptoms are generally perennial. Its diagnosis is not easy because of its similarity to such organic diseases as gastritis, peptic ulcer, chronic gallbladder disease and such functional diseases as gastric neuroses. In the absence of evidence pointing to either organic or functional disease of definite origin other than allergy, a presumptive diagnosis of gastric allergy may be made providing the following factors are elicited:

1. A family history of allergy
2. A history of some other allergic manifestation, past or present
3. A history of food dislikes
4. Definite knowledge of a specific relation of symptoms to the ingestion of particular foods
5. Demonstrable, characteristic allergic changes in the skin or accessible mucous membranes (nasal smears positive for eosinophlis)
6. Positive skin reactions

Two types of chronic allergic indigestion are observed. In the first it is noted that certain foods precipitate symptoms within a few minutes to an hour after their ingestion. The symptoms are of all degrees of severity and consist of gaseous eructations, pyrosis, severe headache, abdominal discomfort and distention, epigastric pain and at times nausea and vomiting. The patient frequently is aware of definite food idiosyncrasies; skin tests are usually positive, and the administration of epinephrine is a very satisfactory therapeutic test in its effectiveness in relieving symptoms. This type is often confused with peptic or duodenal ulcer.

In the second type the symptoms usually ocur at night, several hours after food is taken, and are practically always associated with chronic bronchial asthma. As in chronic appendicitis or gallbladder disease, there may be diffuse, dull abdominal pain or pain localized to the upper or the lower right quadrant of the abdomen, eructations, loss of weight, anorexia, insomnia and neurasthenia, often relieved by fasting or restricted diet. Because the symptoms may simulate peptic or duodenal ulcer or chronic intestinal obstruction, resort is had to the usual treatment for these conditions, including operation. When despite such treatment the symptoms continue, one must consider allergy as a possible etiologic basis for the complaint.

Although allergy generally produces no demonstrable changes in the gastrointestinal tract, there are those who believe that such changes are possible. Thus, Kern and Stewart[15] reported a definite relation between gastric ulcer and food allergy in a small number of cases. Rowe expressed the opinion that canker sores in the mouth produced by foods may be likened to ulcers in the mucosa of the stomach or duodenum. Gay[13] reported observations similar to those of Kern and Stewart. One must not lose sight of the fact, however, that allergic persons are just as susceptible to nonallergic organic diseases of the gastrointestinal tract as are nonallergic persons.

When definite and positive skin reactions are correlated clinically with the relief of symptoms by removal of the offending foods from the diet or with the reproduction of symptoms by addition of those foods to the diet, then it may be presumed that such symptoms or organic changes are the result of allergy.

Acute Conditions Within the Abdomen; Henoch's Purpura; Allergic Symptoms Simulating Acute Intestinal Obstruction, Acute Appendicitis and Other Acute Abdominal Infections.—The essential characteristics of the syndrome known as Henoch's purpura were first described by Osler, who expressed the suspicion that they might be evidence of an anaphylactic process. Osler[17] laid particular stress on the occurrence of what he called "exudative lesions," such as urticaria, angioneurotic edema and purpura in the presence of visceral crises. More recently Alexander and Eyermann[1] and others have expressed the opinion that there seems to be a close relation between Henoch's purpura and acute intestinal allergy, pointing out that similar lesions are found in both conditions. In both, spasm of portions of the intestinal musculature is demonstrable with the x-ray, and peritoneal urticaria and hemorrhage with edema of the bowel wall are demonstrable on laparotomy. Many patients with Henoch's purpura have a family history of allergy, and often there is a coexistent history of eczema, urticaria, hay fever or asthma. Many patients also give excellent reactions to skin tests.

The clinical symptoms of Henoch's purpura or acute intestinal allergy are abdominal pain (simulating that in acute conditions of the abdomen), distention, spasticity (but rarely rigidity) of the abdominal muscles, nausea, vomiting and visible associated exudative lesions, such as urticaria, angioneurotic edema and purpura. Attacks are often periodic and may occur at any age. The abdominal pain is at first dull and nagging, becoming colicky and crampy and when severe causing shock and collapse. Pain may start on either side of the abdomen, become localized or shift from one area to another. Shoulder pain often is the initial symptom, and later lumbar pain may be complained of.

The blood may show from 15,000 to 30,000 leukocytes, and the eosinophils may be increased to 20 per cent or more. The polymorphonuclear neutrophils are rarely increased in proportion to the leukocytes present.

Epinephrine furnishes an excellent therapeutic test in the presence of Henoch's purpura and will usually relieve the symptoms of pain and intestinal spasm in a few minutes.

Derived from the foregoing concept of the allergic nature of Henoch's purpura with abdominal visceral crises is the concept that the same process may occur in a milder degree—that is, reaching the stage of hemorrhage—both processes being considered as different degrees of the characteristic increased capillary permeability of allergy.

As has been pointed out, in 1904 Osler,[17] discussing angioneurotic edema of the bowel, stated: "The possibility of mistaking visceral crisis for appendicitis, intussusception or obstruction of the bowel and handing the patient over to the surgeon is by no means remote." Experience has more than justified this statement. On more than one occasion we have seen localized edema of the appendix and cecum exposed by a laparotomy performed on the basis of a diagnosis of acute appendicitis.

Acute intestinal allergy is frequently characterized by the sudden onset of severe, even excruciating, pain diffused over the entire abdomen, which may later localize itself anywhere in the abdomen, accompanied by marked tenderness and distention. Rarely is rigidity observed. There are usually nausea and vomiting, and diarrhea and shock may occur. Occasionally there are angioneurotic edema of the lips and face and generalized urticaria. The temperature is usually normal at the onset, later rising as high as 102 F. A feature of this syndrome is the complaint of pain in the extremities (shoulders, hips, feet) and headache.

In the differential diagnosis of this condition, which may readily lead to laparotomy, it is essential to recognize the patient as allergic and to note that the point tenderness and muscle spasm are far too mild for the ordinary acute inflammatory condition in the abdomen.

The acute type of allergy of the intestines occurs usually in persons having a low threshold with an allergic balance which is easily disturbed. Such persons have a high degree of sensitivity and are frequently aware of an offending allergen. Positive skin reactions are usually obtained, but negative reactions need not preclude a diagnosis of allergy. Duke[9] expressed the belief we hold, that epinephrine furnishes a good therapeutic test because the severest symptoms will yield to it. Cooke, on the other hand, failed to observe relief through its use.

Chronic Abdominal Pain; Allergic Symptoms Simulating Chronic Appendicitis, Chronic Intestinal Obstruction, etc.—Chronic abdominal pain due to allergy has been discussed in connection with anorexia and vomiting in infancy and childhood and with allergic dyspepsia. In both these conditions the allergic process presumably involves only the stomach. Chronic pain related to allergy of the intestines is more diffuse and less intermittent and is usually described by the patient as a nagging sense of abdominal distress or discomfort with mild nausea. Frequently a dull occipital or migraine-like headache accompanies these symptoms. From time to time there are acute exacerbations of severe, colicky abdominal pain without fever or abdominal rigidity and generally without localization.

We are of the opinion that patients with this syndrome are allergic persons whose tolerance is relatively high. Only when an overwhelming dose of allergens upsets the allergic balance do the acute symptoms arise. Because of accompanying sensitivity to pollens many of these patients have abdominal symptoms only during the hay fever season, the exposure to pollens providing a sufficient added burden to overcome the patient's tolerance and thus upset his allergic balance.

Mucous Colitis; Spastic Colitis.—By the inclusion of mucous colitis and spastic colitis in the discussion of gastrointestinal allergy there is no implication that all occurrences of these syndromes are of allergic origin. Nevertheless, their occurrence is common in allergic persons; they may be produced at will in susceptible allergic patients by the administration of offending foods or the injection of offending pollens, and they may be relieved by a specific regimen based on the diagnosis of allergy. The relation to bronchial asthma was pointed out by Hertz[14] in 1910 in the observation that "A similar type of individual is liable to the two conditions, both of which may sometimes occur in the same person either alternately or simultaneously, or in different members of a family." Vaughan[27] pointed out that in both the outstanding features are smooth muscle spasm and increased secretion of mucus, and that the parasympathetic innervation of the lower half of the colon is of the same type as that of the bronchial tree.

Allergic mucous colitis occurs at all ages, generally between thirty and forty, and more frequently in females than in males. It is usually associated with other evidences of allergy, particularly in persons possessed of a neurasthenic temperament. The symptoms complained of vary, though usually there are headache (frequently migrainous), malaise, abdominal pain and tenderness, intestinal cramps and the passing of large amounts of mucus. Alternating constipation and diarrhea are common, and the patient is frequently under-nourished, neurotic, mentally depressed and easily upset emotionally. Sigmoidoscopic examination reveals no evidence of inflammation, the picture resembling that revealed by the bronchoscope in the presence of asthma—that is, a pale edematous mucous membrane secreting large amounts of mucus. *X-ray* studies may reveal disharmonic tonus and spasticity of the colon. Skin tests in the presence of allergic mucous colitis are usually positive, particularly when there is a positive hereditary history or an associated allergy.

Pruritus Ani.—Pruritus ani occurs occasionally as a localized and independent symptom of allergy, and allergy should always be taken into consideration when such an isolated symptom presents itself. More frequently, however, pruritus ani is one symptom of a group related to allergy either of the digestive tract or of the skin.

The treatment of the isolated symptom, as of all other allergic symptoms, is based on the recognition of its allergic nature and the results of skin tests to foods, inhalants and contact substances.

DIAGNOSIS

The diagnosis of gastrointestinal allergy goes hand in hand with the diagnosis of allergy in general. As has been brought out before, not all gastrointestinal symptoms in obviously allergic persons are due to allergy, but many gastrointestinal symptoms in persons not obviously allergic are due to allergy. For the former type one must rule out allergy and demonstrate a reasonable nonallergic cause; for the latter one must rule out all possible nonallergic causes and recognize the presence of allergy. Failure to recognize allergy in the presence of gastrointestinal disturbances will lead to serious maltreatment from errors of either omission or commission.

We have already spoken of the value of a properly taken family history as a clue to the recognition of allergy. In but few fields of medicine is the significance of a positive family history so great.

The allergic patient rarely complains of symptoms referable to only one anatomic subdivision of the body. If the present complaint is referred to the gastrointestinal tract, one will, on careful questioning, usually elicit a story of a previous or concurrent obviously allergic ailment elsewhere. Interrogation as to food dislikes, dietetic vagaries and drug idiosyncrasies will frequently give clues to a diagnosis of allergy.

Physical Examination.—The physical examination should aid in excluding the possibility of organic or functional disease other than allergy. Certain signs characteristic of allergy frequently go unobserved. These are the mild urticarial or eczematous lesions and the characteristic changes of the upper part of the respiratory tract to which we have previously referred. The importance of the latter changes as an aid to the recognition of allergy cannot be over-emphasized, and it behooves all who would be aware of allergy to become familiar with them.

Specific findings in allergic disturbances of the gastrointestinal tract may be divided into those associated with acute and with chronic disorders:

ACUTE TYPES

1. Edema and itching of lips, tongue, etc.
2. The constant presence of abdominal tenderness, usually diffuse but when localized likely to shift from one region to another
3. The constant presence of abdominal distention
4. The constant absence of abdominal rigidity
5. The temperature, generally normal at onset but rising later in an attack
6. Cutaneous eruptions, such as urticaria, purpura, angioneurotic edema, eczema

CHRONIC TYPES

1. Chronic urticaria or eczema
2. Intermittent tenderness and dull, cramplike pain
3. The constant absence of abdominal rigidity
4. Intermittent or constant abdominal distention
5. Diarrhea with alternating constipation and mucous colitis
6. The constant presence of evidence of allergy of the respiratory tract

X-ray Studies.—*X*-ray studies in the presence of gastrointestinal allergy do not reveal any specific abnormality. Occasionally pyloric spasm is observed in patients with upper right quadrant or epigastric pain. Abdominal pain with symptoms referred to the region of the colon has been observed by Eyermann[11] to produce disharmonic tonus and spasticity. He reported that the administration of epinephrine gave subjective relief and lessened spasticity. Rowe[22] studied 4 patients who probably had disorders generally classified as chronic with pain referred to the upper right quadrant or epigastrium. His findings were uniform in all cases, *viz.*, gastric retention, marked after three hours and definite after six hours, with varying degrees of pylorospasm. He also observed spasticity of the colon in 3 cases and expressed the belief that these disturbances could be the result of a local or generalized mucosal edema or smooth muscle spasm arising from allergic reactions.

One cannot, except for the foregoing observations, present characteristic *x*-ray pictures of gastrointestinal allergy. The chief value of *x*-ray study lies in the significance of the negative evidence which it gives, an important consideration in eliminating organic disease of this tract.

Laboratory Studies.—Blood studies are important. With the acute manifestations leukocytosis may occur, though usually the leukocyte count is normal at the onset, rising during the attack. Contrary to reports in the literature, the eosinophil count may be normal at the onset and during the early part of the attack, increasing as the attack subsides and reaching its highest peak with recovery.

Urine examinations offer no positive information.

Gastric analyses and examination of feces are helpful only in eliminating the possibility of organic disease.

Nasal smears are a valuable aid in diagnosis. The presence of eosinophils identifies the patient as allergic and therefore raises the presumption that the alimentary tract symptoms may be allergic also. (The technic for the study of nasal smears may be found in any textbook on allergy.)

Skin Tests.—The essential purpose of the skin test is to determine the specific excitant or excitants that may be responsible for the patient's symptoms and to corroborate the diagnosis of allergy. A complete series of skin tests must be considered necessary routine in the study of any allergic person. The choice of allergens and the number employed depend entirely on the history and the clinician. Generally it is advisable to test with all important and common food and environmental allergens, particularly where no clue is obtainable from the history.

The results of skin tests must be interpreted with caution when history, physical examination and laboratory and *x*-ray studies show the presence of organic disease, functional nervous disorders or congenital anomalies of the gastrointestinal tract.

The accepted methods of skin testing are: (1) cutaneous (scratch or prick) method; (2) intradermal or intracutaneous method; (3) passive transfer or indirect method.

Cutaneous (Scratch or Pick) Skin Testing.—This is the best method in the hands of the average clinician, because of its simplicity, the freedom from danger of constitutional reactions and the general absence of pseudoreactions. It is a very satisfactory procedure and gives valuable information, particularly for work with active allergens on a sensitive patient.

Technic: In adults the skin of the forearm and in infants and young children the skin of the back is the location of choice. The skin is cleansed with alcohol and dried; then small superficial scratches or abrasions about $\frac{1}{8}$ inch long are made through the epidermis with a scalpel, chalazion knife or needle. Care should be taken not to draw blood. The scratches should be 1 inch apart to avoid contamination by the allergen of the adjoining scratches, as well as to insure clear definition of positive reactions. Allergen solutions are applied directly to the scratches and rubbed in gently with a toothpick. If, however, the allergen is in powder form, a drop of a diluent, usually hundredth normal sodium hydroxide or saline solution, is placed on each scratch, and the powdered extract added and mixed with a toothpick and allowed to remain on the scratch. A control application of 1 drop of diluent is advisable. In the prick method the allergen is first placed on the skin and the skin pricked through the allergen. From 8 to 10 sites on each arm or side of the back are available, depending on the size of the surface and the age and sensitivity of the patient. Reactions usually reach their maximum in fifteen to twenty minutes. After such a period of waiting the material is cleaned off with cotton and the reaction read.

Intradermal Method.

Technic: The most satisfactory location is the outer aspect of the arm, which should be free of any constricting clothing. The skin is cleansed with alcohol. With a tuberculin syringe, a sterile solution of allergen (0.01 cc.) is injected into the outer layers of the skin, with a 26-gage, $\frac{3}{8}$ inch hypodermic needle. The tests should be arranged in single rows 1 inch apart, 10 tests on each arm usually being made at one sitting. After the injection a small white pinpoint of infiltration is observed, and the reactions usually appear and reach their maximum in from five to fifteen minutes. A control application of diluting fluid is always used on each arm. This method of testing requires more skill than the scratch method, and the possibilities of constitutional reaction are greater, as are the number of pseudoreactions. However, it is a more delicate and more accurate test, and reactions occur more quickly. The testing materials are allergens which have been made into dilute solutions, usually 1:1,000, and tested for sterility. The extracting fluid is either buffered salt, Coca's or dextrose solution. Antigens should be made fresh at frequent intervals to be certain of their activity from an antigenic standpoint.

The Indirect or Passive Transfer Method of Testing (Prausnitz-Küstner).—This is only mentioned here. It has only a limited application in gastrointestinal allergy. The technic is available in the several textbooks on allergy and immunology. It may be very useful, particularly in experimental studies and whenever direct skin testing methods are impossible or inadvisable because of skin lesions that may be contagious or are so diffuse as to make it impossible to find clear areas to test. The method is useful in studying infants and children either too young or too small to be tested by other methods.

The interpretation of skin tests is important, though we can discuss it only briefly here. Only by experience can one learn to interpret reactions properly. However, certain general rules may be established: One must always compare the reactions in the tested and in the control site. Any erythematous area or urticarial wheal equal to the control should be considered questionable (+) and that particular allergen should be retested. An area of erythema or wheal slightly larger than the control is called ++. Marked erythema with wheal and pseudopodia up to 0.5 centimeter in diameter is +++. Erythema with wheal and pseudopodia over 0.5 centimeter is ++++.

Since skin tests are frequently negative in patients suspected or known to have food sensitivity, Rowe[21] advocated the use of trial or elimination diets for diagnostic purposes. He contended that positive skin reactions often have no clinical significance and that therefore only through diet trial can one establish both the cause and a diagnosis. Not all workers are in accord with this belief. Many trial diets have been offered.[28] Rowe suggested that each elimination diet be continued from ten days to four weeks. If there is then no relief, another elimination diet must be prescribed. Should there be a loss of weight, the allowed foods must be increased. If the cause is determined through this procedure and the patient remains free of symptoms, other foods, one to three at a time, from the remaining elimination diets are tried every four to seven days.

Vaughan[29] has suggested the leukopenic index as useful in the diagnosis of allergy. Recently Loveless,[16] Brown and Wadsworth[4] and others have proved it unreliable.

TREATMENT

The treatment of allergy that affects the gastrointestinal tract is similar in principle to that advised for allergic diseases in general and may be divided into two main divisions:

1. Discovery of and elimination or avoidance of the etiologic allergens.
2. Specific therapy in an effort to desensitize against those allergens that cannot be eliminated from the diet or environment or with which contact is unavoidable.

The elimination and avoidance of etiologic allergens on the basis of information obtained from the patient's experience or from skin testing offers a satisfactory means of obtaining lasting relief. Since most gastrointestinal allergy is due to foods, complete exclusion from the diet of the offending foods is indicated. Thus, if sensitivity to egg is demonstrated through skin testing and clinically corroborated, the patient must be advised of that food's widespread use in cooking and warned against prepared foods in which it might be contained. Prepared foods are now so numerous and their constitution so complex that several texts on allergy include extensive lists of their analysis. Unless these are consulted, even honest efforts in the elimination of foods will often result in unsatisfactory results.

Diet trial has been recommended by Rowe[21] and others who are enthusiastic about their success with this procedure. On the other hand, many ardent workers in allergy and internal medicine have not been as successful, even though they carefully carried out the procedure suggested by him. No harm can come and perhaps some good may result from its use when specific skin reactions are absent or cannot be corroborated clinically. Rowe's trial diets are described in detail in his text on allergy.[23]

Oral desensitization consists of administering the food by mouth, either intact or in the form of a pure protein allergen. The initial dose usually consists of a quantity less than that which fails to give a positive skin reaction, regardless of how slight it may be; the dose is then gradually increased each day until the patient is taking a quantity comparable to the amount the ordinary person takes. This method has been recommended particularly for egg, wheat and milk sensitivities, but may be used for desensitization to inhalants as well. The method is not devoid of danger, for severe reactions with consequent loss of tolerance have been observed even though the dose was so weak that by skin test the reaction was negative. Successful results by this method have been reported by Schloss,[24] Walker,[30] Stuart and Farnham[26] and others. However, the method has not been successful in the hands of most workers and is not generally used. Objections to the method are: (1) uncertainty of success even when carried out over a long period; (2) difficulty of accurately measuring the dose; (3) impracticability for adults who eat in restaurants, and (4) loss of tolerance after reaction to an over-dose. The elimination of offending foods based on the results of skin tests is more practical and usually results in permanent desensitization.

Hypodermic desensitization to foods may be attempted, the principle being the same as that used with inhalants. It is rarely employed, although cases have been reported[8] in which benefit was obtained by this method of treatment. The method is not without danger, takes a long time even if successful and economically is too expensive for the average patient, as compared with the ease and total absence of danger in treatment by elimination of the offending food.

In only exceptional cases, as in certain occupational groups—bakers, confectioners and grocers—sensitive to the food materials with which they work, should desensitization to foods by the hypodermic method be attempted.

The elimination and avoidance of contact with the inhalant group is also possible, but neither so certain nor so complete as with foods. Even though the patient may remove feathers, animal, orris and pyrethrum from his own environment, he is still exposed to them outside his own home. Desensitization to inhalant allergens is, therefore, best accomplished by the injection method.

Symptomatic treatment of gastrointestinal allergy should include measures similar to those employed for nonallergic gastrointestinal disorders. In addition, 1:1,000 epinephrine in doses of 0.5 to 1 cubic centimeter by hypodermic usually acts immediately, its effect lasting from one to three hours. For the acute types a single dose will often relieve the individual attack and not require repetition until the next attack. The drug has little if any value for the chronic types. It may be employed as a therapeutic test in cases of suspected allergy.

Ephedrine is an alkaloid obtained from ephedra vulgaris; its action in many respects is similar to that of epinephrine. It is easily absorbed in the gastrointestinal tract and may be given orally. The preparations commonly used are the hydrochloride and the sulfate in doses of $\frac{1}{4}$ to $\frac{3}{4}$ grain at three to four hour intervals. The drug is of value for both chronic and acute gastrointestinal allergy. It may be used particularly to prevent or abort attacks that have a definite periodicity.

Atropine and belladonna have the same limitations and indications for allergic gastrointestinal diseases as for the nonallergic types. Except for the gastric-spasm type of allergy, they are of little value.

Opium and its derivatives are merely mentioned in passing, since they have little if any place in the treatment of allergic digestive disturbances and since the aforementioned drugs give satisfactory palliative results.

General Measures.—The successful treatment of gastrointestinal allergy primarily requires dietetic control based on the results of skin tests. Such control should eliminate all offending foods, give a well balanced diet, maintain weight and furnish the required vitamins and minerals. In order to avoid new sensitizations the diet must not emphasize any single food too greatly. Success with such a regimen often depends on constantly keeping in mind that the allergic state of the patient is variable and that sudden changes are common. To guard against overlooking this phenomenon, one must insist on the patient's keeping a dietetic diary, and retest the patient when the diary shows the recurrence of symptoms despite faithful adherence to the diet.

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CHAPTER XLV

ENDOCRINOLOGIC MANIFESTATIONS IN THE GASTROINTESTINAL TRACT

THE AUTONOMIC NERVOUS SYSTEM IN RELATION TO THE GASTROINTESTINAL TRACT

The relation of the endocrine glands to the gastrointestinal tract cannot be intelligibly presented without recognition of the intimate relation that exists between the autonomic nervous system and the gastrointestinal tract and the autonomic nervous system and the ductless glands. The functions of all three systems are interrelated and to a greater or lesser degree dependent on each other.

The autonomic nervous system is divided anatomically into two separate and distinct parts which are physiologically antagonistic to each other when stimulated and which counterbalance each other when not stimulated. These two divisions are the parasympathetic and the sympathetic.

The Parasympathetic Nervous System.—The anatomy of the parasympathetic nervous system is covered in Grinker's contribution to this book.

The Sympathetic Nervous System.—The sympathetic nervous system consists of two nerve cords known as the ganglionated cords, lying one on each side along the entire ventral surface of the vertebral column from the atlas to the coccyx, where they converge and unite in a single unpaired ganglion known as the coccygeal ganglion.

Other structures associated with the sympathetic nervous system are the collateral ganglions, such as the semilunar ganglions of the solar plexus about the celiac axis, the renal, the mesenteric and the hypogastric plexus and the adrenal cortical tissue.

Stimulation of the sympathetic nervous system causes contraction of the dilator muscle of the iris, dilating the pupil. It accelerates the heart and is inhibitory to the smooth musculature of the trachea and bronchi.

It is inhibitory to the esophagus, pyloric half of the stomach, small intestine, large bowel and sigmoid flexure.

It inhibits the secretion of the bronchial mucous glands, the salivary and gastric glands and pancreas, but stimulates the sweat glands to secrete.

It contracts the vessels of the abdominal viscera (splanchnic area) and the bloodvessels of the mucous membranes of the head and of the skin. It contracts the pilomotor muscles, raising the hairs.

Human Autonomic Pharmacology.—Myerson[51] and his associates at the Boston State Hospital have stated the following theory:

> The autonomic nervous system manufactures chemical substances which regulate visceral activity. The autonomic activity is the resultant of three sets of chemical substances: (1) sympathin which is the active agent in bringing about what are here called adrenergic effects and which is mainly formed at the junction between the second sympathetic neuron and the reacting cell. (2) Acting in a balance to this chemical is acetylcholine which is mainly produced by the parasympathetic neurons and operates at the junction between the neurons and the junction of the second parasympathetic neuron and the reacting cell. (3) Cholinesterase is

an enzyme, the function of which is to hydrolyze or destroy the acetylcholine. It is present in the tissues and in the blood, and acts so as to render the activity of the parasympathetic enzyme, acetylcholine, intermittent in its activity. Thus, there is a balance, on the one hand, between the adrenergic substances of the sympathetic nervous system and the cholinergic substances of the parasympathetic nervous system, and on the other hand, a more local balance between the acetylcholine and the esterases.

Reflexes in the Autonomic Nervous System.—There are two main classes of reflexes within the vegetative nervous system. In one variety, the centripetal (toward the central nervous system) path runs in a cerebrospinal nerve, and the stimulus on reaching the brain stem is reflected outward along a fiber of the vegetative system. Examples of this class of reflex are the increased flow of saliva on seeing and smelling food during hunger, blushing in embarrassment, tachycardia in fright and the genital reflexes. The second variety of vegetative reflex has both its afferent and efferent limbs running in vegetative paths, *e. g.*, the ordinary movements of hollow organs which are under the control of a peripheral plexus, such as the gastrointestinal tract, uterus, ureters and bladder, all of which contract independently of cerebrospinal stimuli.

The organs, cutaneous and internal, which contain nonstriped muscle or secretory cells are independent of the will. Thus, not only the heart muscle (striped) but many other visceral muscles, *e. g.*, those of the stomach, intestine and spleen, have the power of automatic rhythmic contraction. Nevertheless, visceral activities can be profoundly influenced by the central nervous system through emotional stimuli such as anger, fear, pleasure, surprise, shame and sexual excitement.

Thus, for example, the processes of digestion are especially sensitive to emotional states, so that pleasurable experiences, an artistically laid table, a charming host or guest or a melodious orchestra promotes digestion, whereas painful or disagreeable sensations inhibit it.

Who has not partaken of a bounteous meal and afterward become, for some unexpected reason, greatly frightened or angered and suffered from acute indigestion, characterized by the sensation of a great weight or the so-called lump in the stomach which is distinctly painful?

What has happened in this instance is that the fear or anger has stimulated the sympathetic nervous system, thereby causing it to overact, with resultant checking of gastric secretions and motility. The vessels of the splanchnic area have been contracted and the blood driven to the vessels of the heart, lungs and brain.

Emotional stress, long continued, such as that produced by the modern tendency to speed up all activities for greater efficiency, results in a constant state of nervous tension, with overactivity of the sympathetic nervous system, which in turn inhibits the motor and secretory function of the parasympathetic division of the autonomic nervous system, with consequent nervous indigestion. This disturbed function may at first manifest itself as an uncomfortable sensation in the epigastrium, accompanied by distention, eructation of gas and perhaps pyrosis, occurring within one-half to two or three hours after meals. This is usually relieved by taking some food or alkaline substance, but if the factors, such as worry, unhappiness or financial strain, which are responsible for the autonomic imbalance are not relieved by rest and avoidance of nervous tension, then more serious gastrointestinal conditions may ensue.

A knowledge of Elliot's law of the innervation of a hollow viscus is fundamental in understanding the functional relation between the two divisions of the autonomic nervous system. It may be stated as follows: "When the quiet lodgment of the contents of a hollow viscus is facilitated by the presence of sympathetic inhibitory fibers, there will also be sympathetic motor fibers to the sphincter closing the exit." Examples are the stomach, rectum, urinary bladder and gallbladder.

Explanation: It is necessary for food, especially meat, to remain in the stomach three or four hours so that proper gastric digestion may take place. The parasympathetic chain through the vagus is motor to probably the lower two-thirds of the stomach. If it were motor also to the pyloric sphincter it would produce premature emptying. But this is not the case. The motor mechanism of the pyloric sphincter is under the control of the sympathetic system, the vagus being inhibitory to it.

It must be remembered, however, that the relaxation of the pyloric sphincter is dependent in large part on a reflex mechanism. Serjukow has shown that the pylorus remains firmly closed as long as the contents of the duodenum are acid. The sensory stimulus would appear to be chemical and provided by the acid of the stomach.

Other well known examples of this innervation are furnished by the rectal pouch and the urinary bladder.

It is necessary daily that the contents of these hollow organs for comfort and convenience be retained for indefinite lengths of time. Therefore, while the parasympathetic pelvic nerve is motor to these organs and inhibitory to their sphincters, the sympathetic nerve is inhibitory to their musculature and motor to their sphincters.

This innervation, according to many physiologists, also is present at the cardiac orifice of the stomach, the sphincter of Oddi (at the opening of the ampulla of Vater in the common bile duct) and the ileocecal valve and produces a valvelike action in the first third of the transverse colon.

The parasympathetic nervous system governs the organs responsible for the accumulation of energy within the body and exercises more or less control over its conservation.

The secretions of the salivary and gastric glands and to a lesser extent of the pancreas, the movement of food through the alimentary tract and its digestion, absorption and assimilation are all influenced by this system.

The results of sympathetic stimulation are catabolic and serve to activate the body for a struggle and to increase its powers of defense, utilizing the reserves of potential energy.

In intense anger or fear the pupils dilate to increase perception of light; the heart beats more quickly and more forcibly to supply the muscles with blood, and the bloodvessels in the visceral area constrict, raising the blood pressure and thus driving the blood from the digestive area, the functions of which are simultaneously inhibited, into the skeletal and cardiac muscles, the lungs and the brain.

The sweat glands are stimulated to cool the body heated by its excessive muscular effort, and the pilomotor muscles erect the hairs in many animals, to render them more alarming.

Effect of the Ductless Glands on the Autonomic Nervous System.—Another factor which greatly influences the action of the two divisions of the autonomic nervous system is the secretion of the ductless glands.

The purposes particularly served by the endocrine glands are that of producing a chemical correlating mechanism and, by the vegetative nervous system, that of maintaining a nerve-correlating mechanism. Tissues can act within any nerve connection, but action for the benefit of the organism as a whole can be brought about only by the correlating mechanism, which unites all parts of the body in such a way that action in one influences action in others.

Epinephrine acts on the neuromuscular end-plates of the sympathetic nerves and produces the same effects as electrical stimulation would, except on the pilomotor muscles and sweat glands. The drug will not cause sweating. Epinephrine mobilizes dextrose by releasing it from its storehouse in the liver, where it exists as glycogen, thereby increasing the sugar content of the blood; increases clotting time by increasing prothrombin; diminishes muscular fatigue and checks the secretion of the digestive glands, and causes tachycardia, increase in cardiac action, anemia of the gastrointestinal and respiratory tracts and rise in blood pressure.

Thyroid secretion (thyroxin) stimulates the adrenal glands; epinephrine stimulates the sympathetic system, and the thyroid in turn is stimulated by the sympathetic system.

Pituitrin (obstetrical) contracts the arteries, with the exception of the renal vessels, and raises blood pressure. It stimulates the splanchnic nerves, especially the lesser ones to the large bowel, bladder and uterus. It may have an inhibitory effect on the secretion of urine, as shown in the presence of pituitary polyuria, of some pituitary tumors and of hypopituitarism. Kamm and his associates[42] (1928) isolated two active principles of the posterior lobe, pitressin and pitocin, which will be discussed more fully in the section on function of the pituitary gland.

In summary: the secretion of all three tends to raise blood sugar and lower carbohydrate tolerance.

The adrenal glands coöperate with the sympathetic system in every way so that the injection of epinephrine imitates the effect of stimulating the sympathetic nerves. The thyroid aids all the catabolic activities of the sympathetic chain, while the pituitary plays a large part in controlling the excretion of urine.

The secretion of the adrenal glands and of the thyroid not only are excited through the sympathetic system but in turn increase the response of other structures to such stimulation. This reciprocation has not been observed in the case of the pituitary gland.

THE GASTROINTESTINAL TRACT

Hormones Affecting the Gingival and Mucous Membranes of the Oral Cavity.—Ziskin,[62] after extensive studies on a large number of monkeys and on women, found that the sex-related hormones exercise a marked influence on the gingival and mucous membranes of the mouth.

He described five forms of "pregnancy gingivitis":

> The first form, and by far the most common, is characterized by bleeding of the gums. On questioning the patient, it may be ascertained that the tendency for the gums to bleed when traumatized by the toothbrush, food, etc., developed after the onset of pregnancy; or, if the symptom were present before pregnancy, it became exaggerated after conception. Hemorrhage is also easily induced by probing.
>
> The next recognizable form is a slight change in the interdental papillae. The

papilla loses its stippled appearance, becoming glossy or "glassy" looking. Its color changes from pink to old rose. There is some edema, creating a mildly puffed appearance. Because of the swelling, the papilla no longer maintains the sharply pointed architecture of a pyramid, but becomes somewhat blunted at the tip. The symptoms are seen early, and if uncomplicated by local conditions, may persist in an unexaggerated state throughout the term. After parturition, the gums generally return to normal without treatment.

In the third type of "pregnancy gingivitis," usually only the free gum margin is involved. It takes on the color and appearance of a raspberry. The highly inflamed tissue bleeds easily on being probed. Its most frequent site is the anterior gums, although it may be found in other locations. This form is designated "raspberry red gums."

The fourth form, a generalized hypertrophy of the tissue, is designated "hypertrophic gingivitis of pregnancy." The interdental papillae become noticeably enlarged, losing their matural contours. The color may vary from an old rose to a deeper, cyanotic hue. In the presence of irritation, the borders may become bright red. The amount of involvement varies. One, a few or many papillae may be involved in one or more sections of the mouth. The tumefaction of the individual papillae is gross in some and slight in others.

The enlargement of the papillae is due in part to edema, but also to hyperplasia of the epithelium. Sometimes, a proliferation tissue forms. As it grows, the normal gum is pushed back, a straight blanched line of demarcation resulting. In some instances, the proliferation tissue, which emerges from the under-surface of the papillae, may grow over and cover in part the crown portion of the teeth. Here, then, is created a favorable site for mouth sordes to collect and act as an irritant, additional proliferation resulting.

In all instances of "hypertrophic gingivitis of pregnancy," the gums bleed easily on being probed, but are seldom, if ever, painful.

The fifth form of "pregnancy gingivitis" is the so-called pregnancy tumor, for the most part confined to a single growth springing up at any point in the mouth. At the outset, it appears to be an overgrown gum papilla. After it has attained considerable size, it resembles an epulis varying from 1 to 2 cm. in diameter, and sometimes larger. It usually has a pedunculated attachment. In color, it is cyanotic, with a bright red border. Often, it interferes with mastication, and the trauma to which it is subjected produces an area of grayish necrosis on parts of the surface. However, in one case studied, the entire growth was blood red.

All forms of "pregnancy gingivitis," if not properly treated, are likely to recur with subsequent pregnancies, or set up some other form of gingivitis after parturition.

Changes described as pregnancy gingivitis are not limited to pregnant women. They occur in non-pregnant women, in men, very frequently in boys and girls at about the time of puberty and in women during the menstrual period. However, their most frequent occurrence is at times usually associated with hormonal change: pregnancy, menstruation and puberty.

Blackberg and Ziskin treated monkeys and women with the various estrogenic hormones, anterior pituitary gonadotropic hormone and pregnancy urine extract (APL).

The estrogenic substances produced the following results: (1) Hyperkeratinization: Where keratin is found normally, namely, on the surface of the alveolar gingivae, this layer was improved. Keratin was also seen on the surface of the areolar gingivae and the oral mucous membranes, areas where none is found normally. In addition, epithelial pearls appeared in the prickle cell layer, a further sign of hyperkeratinization. (2) Hyperplasia of the pickle cell layer of the epithelium: Inflammatory reactions in the subepithelial layer were either reduced to a minimum or entirely absent.

The gonadotropic series produced the following results: (1) An extract from the urine of castrated women (anterior pituitary gonadotropic hormone), when injected into normal female monkeys, had an action on the gums and oral mucous membranes similar to that of the estrogenic hormones. (2) Pyridine extracts of the anterior lobe of the pituitary gland produced in normal female monkeys results coinciding with those of the estrogenic substances. (3) An extract of pregnancy urine (prolan) (APL) had an entirely different effect. When injected into normal female monkeys and into women with dysmenorrhea, the changes occurring in the gums were of a degenerative nature. In the monkeys, the gross findings resembled pregnancy gingivitis. The interdental papillae became markedly enlarged and were old rose color. Bleeding was easily induced, and in some instances spontaneous hemorrhage was seen. In the human group, the gums became inflamed and the interdental papillae edematous and prone to bleeding. More extreme reactions were observed in certain cases: lesions resembling "subacute Vincent's infection" and, in one instance, an acute Vincent infection developed. The gum involvement persisted throughout the treatment period. As a group, the women receiving prolan showed gingival changes strikingly opposed to those found in the group receiving estrogenic substances.

The conclusions to be drawn from this work are that the oral tissues as a whole are influenced by endocrine imbalance, especially in women during pregnancy and the menstrual periods and in boys and girls at the time of puberty. Estrogenic and anterior pituitary gonadotropic hormones produce beneficial results, and APL (anterior pituitary-like hormone) produces degenerative changes.

These findings indicate that estrogenic and anterior pituitary gonadotropic hormones are of value in conjunction with local treatment of abnormal conditions in the gingival and mucous surfaces of the mouth during the periods aforementioned.

Schour[58] has shown the effects of normal and abnormal metabolism, of normal and disordered endocrine function and of certain vitamins on development, calcification and maintenance of normal tooth structure.

Gastrointestinal Principles.—The gastrointestinal principles have a more localized effect and do not seem to have the widespread interrelations that the hormones of some of the endocrine glands have.

The Salivary Secretion.—There is no evidence indicating that a hormonal mechanism is concerned in the secretion of saliva. In the normal person the secretion of saliva is brought about reflexly in two ways: (1) through the stimulation of the nerves of the mouth by contained food or other substances and (2) by the stimulation of some sense organ other than that of taste.

The first salivary reflex is unconditioned. When food is taken into the mouth saliva flows because sensory nerve impulses pass to the salivary center in the medulla, from which secretory nerve impulses pass to the salivary glands, causing them to secrete. Ivy[36] has shown that if lemon juice is placed in the mouth of a dog, saliva flows copiously. If the nerves to the salivary glands are severed one day and lemon juice is applied to the mouth the next day, saliva is not formed. When extracts of the oral mucosa are made and then injected intravenously or subcutaneously, the salivary glands are not stimulated.

The second salivary reflex is conditioned, or acquired, and is initiated through one of the special sense organs other than that of taste, such as that of sight or of smell. If one smells or sees food which one knows from training or experience is pleasant and desirable, then the reflex is conveyed through one or more of these special organs of sense to the brain, and a second impulse passes to the salivary glands over the proper nerves and they are stimulated to secrete saliva.

Saliva is alkaline in reaction and contains an amylolytic ferment known as ptyalin and, according to some authorities, maltase. The daily quantity of secretion of the salivary glands varies in different persons and from day to day in the same person, but the amount is estimated at about 1,500 cubic centimeters. The action of saliva is to moisten the food, render soluble certain components and produce diastatic action (ptyalin acts on starch, splitting it to the disaccharide, maltose), which continues until acidification occurs in the stomach.

The Esophageal Secretion.—The esophagus contains two types of glands, known as the esophageal and the cardiac. The esophageal glands are present from the level of the cricoid cartilage downward, and as they approach the cardia there is some modification, so that they resemble more the glands of the fundus of the stomach. They do not produce any digestive ferments or hydrochloric acid, but supply mucus of alkaline reaction which acts as a lubricant to the bolus when swallowed.

The Gastric Secretions.—Pavlov found that the gastric juice of the dog contained 0.4 to 0.5 per cent of hydrochloric acid. In the human being, after a test meal the acidity normally reaches 0.05 to 0.15 per cent. After histamine injection the acid concentration may reach 0.4 to 0.5 per cent.

The gastric juice contains mucin and the digestive agents hydrochloric acid and pepsin, which act on proteins; rennin, a milk-coagulating enzyme; a small amount of lipase, which digests fats, and, according to some authorities, traces of invertin.

Ivy[36] described three phases of gastric secretion when considered from the standpoint of stimulation: (*a*) the cephalic phase, (*b*) the gastric phase and (*c*) the intestinal phase. When food is seen, smelled or tasted in the presence of appetite, nerve impulses pass to the brain and then to the stomach by way of the vagus nerves, causing the so-called psychic secretion of gastric juice. This phase is entirely nervous. The gastric phase is initiated by distention of the stomach and by the secretagogs present in the food or produced by its gastric digestion. The intestinal phase of gastric secretion is initiated by secretagogs acting on the mucosa of the intestine. Whether they act by causing a hormone to be produced or by being absorbed into the blood is not certain.

A humoral agent (such as a hormone or a secretagog) for stimulating gastric secretion has been established[34] by autotransplanting a small pouch of the stomach beneath the skin. When an animal so treated is fed, the transplanted pouch secrets acid gastric juice. Hence, when the animal eats, some substance or substances pass into the blood and stimulate the transplanted pouch. Whether the humoral or blood-borne substance is of the nature of a hormone or of a secretagog is not certain.

Gastrin-histamine.—Bayliss and Starling in 1902 discovered in the upper part of the small intestine a hormone (secretin) which had a powerful effect on the secretion of pancreatic juice. Edkins[18] later searched for a substance which might possibly be the exciter of the gastric secretion. He found that when the pyloric mucosa is ground up and extracted with peptones, dextrose or hydrochloric acid, the extract injected intravenously has a powerful stimulating effect on gastric secretion. Edkins and Tweedy[19] named this principle "gastrin."

The anti-pernicious anemia fraction of liver extract contains a potent gastric secretagog. Its action may be obtained by local application of this fraction to the gastric and intestinal mucosa and by injection intravenously. This hormone, "gastrin," is elaborated chiefly by the mucosa of the pyloric antrum and possibly by the intestinal mucosa when stimulated by solutions of secretagogs.[44]

An acid extract of pyloric mucosa when injected hypodermically stimulates gastric secretion. Crystalline histamine has been isolated from such an extract, and the evidence indicates that it is the sole secretory excitant of such extracts; that is, gastrin and histamine appear to be identical. Apparently, then, histamine is the gastric hormone, if such a hormone exists. If some other substance is the gastric hormone, it has never been extracted from the pyloric mucosa.

Histamine (either the methyl or the ethyl derivative) is the most potent excitant of acid gastric secretion known, and in concentrations that have little or no effect on systemic blood pressure it will stimulate the gastric glands.[41] There is no evidence indicating that histamine has a therapeutic value. It does have a definite role in testing gastric function, namely, to determine whether the gastric glands can secrete free acid. The histamine test is the most rigorous test for differentiating between true and false anacidity.[7]

Antianemic Factors.—Whipple and Robscheit-Robbins[61] (1925) observed that the addition of liver to the diet of dogs having anemia secondary to hemorrhage is efficacious in accelerating blood regeneration.

Minot and Murphy[50] (1926), inspired by the observation of Whipple, added liver to the diet of a person having pernicious anemia, with spectacular success in its treatment.

Castle[11] and his co-workers (1929) showed that pure gastric juice obtained from a normal person and incubated with beef muscle produced the same curative effect as liver did. They also found that gastric juice obtained from a pernicious anemia patient and incubated with beef muscle was ineffective. Castle then concluded that an intrinsic factor in the gastric juice or in the stomach tissue of healthy persons and some animals acts on certain materials in the diet (extrinsic factor) to form a third substance (antianemic factor), which is absorbed by way of the portal circulation and stored in the liver, from which it is carried by the blood to the bone marrow, where it exerts its action in accelerating the maturation of the red blood cells from megaloblasts to normoblasts.

Intestinal Hormones.—**Enterogastrone.**—It has been known for many years that neutral fat inhibits gastric secretion and motility, especially when that fat is in the intestine.

Ewald and Boas[21] (1886), while studying carbohydrate digestion in the stomach by means of the stomach tube, observed that olive oil added to starch paste inhibited the secretion of gastric digestion and delayed evacuation of the stomach in man. A long series of investigations by various workers has been rather completely reported by Ivy.[37] After this original work it was believed that when fat enters the stomach and duodenum gastric activities are reduced by a nervous reflex.

Ivy and his associates[22] did some experiments to show that the inhibitory action of fats on gastric motility and secretion are due to a hormonal mechanism, but they stated that the possibility of a nervous mechanism could not be entirely ruled out. The essential facts showing that a hormonal mechanism exists were described by Ivy[36] as follows: When a small pouch of the stomach is transplanted beneath the skin and a ballon is inserted into the pouch so as to record its movement, it is found that the movements are markedly diminished a few minutes after fat is placed in the duodenum.[22a] The same is true for the acid secretion of the transplanted pouch.[23] A concentrated solution of dextrose or cane sugar acts similarly to fat. Gastric secretion and motility are not inhibited when finely emulsified fat or chyle is injected intravenously. This shows that it is not the absorbed food fat circulating in the blood that causes the inhibition of the movements and secretion of the pouch. Hence, the inhibition must be due to some specific substance or chalone (hormone) secreted by the duodenal mucosa into the blood. Further, extracts of duodenal mucosa have been made which, when injected intravenously or subcutaneously, inhibit gastric secretion and motility.[27]

A substance isolated from the duodenal-jejunal mucosa[43] inhibits gastric secretion and motility. This preparation, "enterogastrone," is free of secretin and cholecystokinin and causes complete suppression of secretion lasting from one to five hours and inhibition of gastric motility for thirty minutes.

The enterogastrone preparations made to date are not toxic, but they are not sufficiently pure for use in man. When the hormone has been prepared in a sufficiently pure form, it may prove to be of value in the treatment of patients having peptic ulcer.

Secretin.—The duodenal mucosa secrets a hormone which stimulates the flow of pancreatic juice.[4] When dilute acid is applied to the duodenum after the nerves to the pancreas have been severed, pancreatic juice still is secreted, and the intravenous injection of acid alone is ineffective. Intravenous injections of acid extracts of the duodenum excite the pancreas to secrete. When the circulation of two dogs is connected, application of acid to the duodenum of one causes secretion from the pancreas of both. Ivy and Farrell[38] later showed that an autotransplanted section of the pancreas is stimulated to secrete when acid is applied to an autotransplanted loop of the duodenum. Secretin appears to be a direct excitant of the glandular cells.

Bayliss and Starling were unable to extract the pancreatic stimulating duodenal hormone with water, so they postulated the idea that it must exist in an inert form and be activated by mild acid. This is known as the "secretin theory": When the acid chyme of the stomach comes into contact with the duodenum, it converts prosecretin to secretin, which is carried by the blood stream to the pancreas, where it exerts its effect. Secretin exists preformed in the mucosa, from which it can be extracted with water, alcohol and other solvents as well as with acid.[47]

The isolation of crystalline secretin was reported by Hammarsten, Jorpes and Agren[29] in 1933. Greengard and Ivy[28] described a method which has resulted uniformly in the isolation of a crystalline salt of secretin which has the properties of the pure compound. This secretin compound is in the form of a crystalline picrolonate, C_3H_3ON.

Crystalline secretin stimulates the liver to secrete bile.[59] The crucial experiment proving this was performed on animals deprived of the pancreas and gastrointestinal tract, so that the increase in flow of bile could not be secondary to increased activity of the pancreas and intestine. The cholagog action of secretin, however, is not as marked as that of bile salts.

Formerly it was thought that the secretion of pancreatic juice was excited by a nervous reflex producing vasodilatation of the pancreatic vessels. Mellanby[46] has maintained the opinion that pancreatic secretion is markedly influenced by the nerve supply to the pancreas. After his experiments, he stated:

> The vagal secretion, though thick and scanty, is particularly rich in ferments. Indeed the secretion of these is apparently entirely under vagal control. The chief, if not the only, effect of secretin, on the other hand, is to cause the secretion of the water, and inorganic constituents, *e. g.*, the bicarbonate of the pancreatic juice. Vagal stimulation causes exhaustion of the zymogen granules. Only after repeated injections of secretin do histologic changes of a similar nature appear, and these are always less pronounced than those following nerve excitation. Apparently then, the extrusion of the colloidal zymogenous particles from the cells into the alveoli is normally controlled by nervous impulses. The hormone, on the other hand, causes a flow of alkaline fluid which serves to flush the alveoli, to thin the juice rich in organic materials and sweep it along the ducts. Under certain circumstances a small secretion of pancreatic juice may be obtained by stimulation of the splanchnic nerve. This is probably a vascular effect. Pavlov has shown that there is a psychic element in the control of pancreatic secretion. Though the effect is much less than in the case of gastric secretion, sham feeding was found very definitely to increase the pancreatic flow.

Cholecystokinin.—Nerves from the parasympathetic and sympathetic divisions of the autonomic system are supplied to the gallbladder, but stimulation of these nerves in the dog and the cat produces only a slight temporary contractile effect. Apparently the principal stimulant for contraction and evacuation of the gallbladder is the hormone cholecystokinin, the presence of which was first (1928) demonstrated by Ivy and Oldberg.[40] This hormone is closely related to secretin chemically, but the two may be separated by an appropriate chemical procedure.

This hormone is produced when dilute acids and fatty acids come in contact with the duodenal mucosa. The essential facts demonstrating the existence of such a hormone follow: When extracts of duodenal mucosa were made and injected into human and canine subjects, the gallbladder contracted and evacuated. Further, when the circulation of two dogs was connected and acid placed in the duodenum of one, the gallbladder of both animals contracted. The intravenous injection of acid or of finely emulsified fat or chyle did not cause the gallbladder to contract. This shows that neither the absorbed acid nor the products of the digestion of fat act as humoral agents for gallbladder contraction and evacuation.

Ivy[35] stated that the most effective excitants for production of the hormone are acids and fats acting in the upper part of the intestine. These substances have little or no action in the lower part. All fats are effective, but egg yolk and cream appear to be the most active. Proteins, particularly meat, rank next, and carbohydrates have little, if any, action.

Enterocrinin.—A hormone obtained from the mucous membranes of the small and the large intestine[52] excites the glands of the small intestine to secrete succus entericus. This hormone is called enterocrinin. The secretagog activity of crude extracts is not directly related to blood pressure changes, because nonvasodilating enterocrinin has been obtained.

Enterocrinin does not excite the pancreas, hence it is separate and distinct from secretin. Its presence in the colon suggests a possible effect on the function of this organ, but no work has been done along this line. However, a few preliminary experiments have showed that the secretion of the ileum is increased by administration of this hormone.

Incretin.—Rather strong presumptive evidence[39] indicates that the duodenal mucosa produces a hormone that stimulates the pancreas to secrete insulin. In the intact animal, certain fractions of the duodenal extract cause a decrease in the hyperglycemia induced by dextrose or by epinephrine, regardless of the mode of administration. The substance also appears to have a direct hypoglycemic property, since it lowers the blood sugar level in depancreatized dogs.

Besides the aforementioned intestinal hormone substances, the pancreatic juice, which is discharged into the duodenum, contains the following ferments: trypsin, a proteolytic enzyme; amylopsin, which hydrolyzes starches; lipase, a fat digestant; rennin, and maltase.

HORMONES IN RELATION TO ULCER OF THE STOMACH AND DUODENUM

Probably the one factor of greatest importance in gastric and duodenal ulcer, and the one that has received the most study, is hydrochloric acid. It is of basic importance in any discussion of its etiology that peptic ulcer occurs only in those portions of the alimentary tract in which the mucous membranes come in contact with the gastric juice. Mann[45] stated:

> If the acid-alkali balance at the pylorus is broken, *i. e.*, if the acid gastric content is caused to be expelled into an intestinal loop that does not have alkalizing protection, a chronic peptic ulcer will develop in the intestinal mucosa at the site where the gastric contents impinge. This condition can be produced in either the functioning intestinal tract or in an isolated loop anastomosed to the stomach. It never occurs in a mucosa not exposed to acid gastric content.

Brown[8] expressed this opinion:

> There can exist no question that the peptic action of the gastric juice plays an important role in the pathogenesis of ulcer. Chronic gastric and duodenal ulcer have been described in patients reported as having no hydrochloric acid secretion, but it is very doubtful whether this is actually true. . . . In this connection it is significant that chronic ulcer is never found in pernicious anemia, a malady invariably associated with total absence of gastric secretion. There is no convincing evidence to indicate that chronic gastric and duodenal ulcer ever occurs in the absence of secretion of hydrochloric acid and pepsin. The lesion is in fact, as well as in name, peptic ulcer.

Action of Gastric Juice on Living Tissues.—Normally the gastric mucosa is resistant to the digestant action of the gastric juice. It is a common assumption that this resistance is due to a specific resistance not possessed by other living tissues, and which is entirely absent after death.

Dragstedt and Vaughn[17] sutured segments of the duodenum, ileum, colon and such organs as the spleen, kidney and pancreas into large openings in the stomach wall, so that they would be subjected to the action of gastric juice. The capsules of the transposed organs were first removed, so as to permit access of the gastric content to the parenchyma. In no case were these tissues digested. Neither were they digested when exposed in a similar manner to the action of the secretion of the first portion of the duodenum. These authors were convinced that there is a widespread resistance to the corrosive action of the gastric and duodenal content on the part of tissues and organs whose blood supply is not interfered with.

However, they emphasized that the experiments yielded data on the resistance of tissue only to the normal gastric content, and not to pure gastric juice, for there is a significant difference between the two with respect to both acid and enzyme content. The concentration of free hydrochloric acid in the stomach contents of a normal man examined one hour after the administration of an Ewald meal varies between 30 and 60 clinical units, whereas that in the pure gastric juice secreted by the isolated stomach of the dog remains practically constant at about 135 units. Carlson[10] gave a similar figure for the acidity of the pure undiluted gastric juice of man.

Further experimental evidence indicates that this pure gastric juice can digest any living tissue and that an ulcer may be expected to develop in any portion of the gastrointestinal tract that is long exposed to a content that resembles it in acid and enzyme concentration.

Dragstedt found that if the organs which remained intact were implanted in a similar manner in an isolated stomach pouch, where they were exposed to the action of pure gastric juice, they were promptly digested. Also, if pure gastric juice was caused to flow into the empty jejunum or ileum, the mucosa was digested and an ulcer formed. If the stomach was isolated from the gastrointestinal tract so that its blood supply and vagal innervation were but little interfered with and so that the gastric juice secreted was not promptly drained away but remained in contact with the gastric wall for a time, the gastric mucosa then was digested away and chronic progressive perforating ulcers developed that anatomically were indistinguishable from the clinical lesion.

This work makes it unnecessary to postulate a specific loss of resistance to account for ulcers of the stomach proper.

Effects of Pituitary Extracts on the Gastrointestinal Tract.—Experimental Production of Peptic Ulcer.—Besides the experimental methods for producing peptic ulcers reported by Dragstedt, approximately a score of other methods for their artificial production have been described by various workers.

Pituitary extracts, especially those of the posterior lobe, cause ulcerations in the gastric and intestinal mucosa of the guinea pig and the rabbit.[25] Necrosis of the entire acid-bearing area of rabbits' stomach occurs twelve to fifteen hours after the administration of 200 to 800 international units of either posterior pituitary extract or the pressor fraction (pitressin) alone, but not with the oxytocic principle of the posterior lobe of the pituitary.[14] Chronic gastric ulcers were produced on the greater curvature of the stomach by repeated administration of pituitrin, but the development of these could be prevented by rendering the gastric contents alkaline.[13] Also large doses of posterior pituitary extract completely inhibited the secretion of gastric juice in response to histamine stimulation for six hours. A reduction of gastric secretion and hydrochloric acid was demonstrated in both man and the dog by the use of posterior pituitary extract.[31]

Metz[48] found

> that by injecting twenty-five international units of posterior pituitary extract per kilogram of body weight into experimental animals, a permanent lesion of the mucosa of only the fundic stomach was produced in every instance. This lesion probably forms in the following sequence: after a period of vascular constriction the widespread edema (produced by the pituitrin) of the gastric and duodenal mucosa subsides everywhere except in the fundus, but there the distinctive pathology, which is a swelling of the parietal cells, is lasting, with the resultant necrosis hemorrhage and ulceration.

However, he concluded that "this constant lesion produced in the fundus by the injection of large doses of pituitary extract, is in no way similar to peptic ulcer as seen in man."

Metz and Lackey[49] studied several cases of active duodenal ulcer which had the unusual accompanying symptom of a mild but definite unexplained polyuria with nocturia. They were unable to find any previously recorded mention of this association. Entertaining the belief that the ulcer is only the apparent part of a systemic disorder the cause of which is unknown, and with the cause of the polyuria and nocturia in these cases of duodenal ulcer unaccounted for, they decided to observe what effect might be produced on the ulcers by treatment for short periods with posterior pituitary extract in the same way that severe diabetes insipidus is treated on the average.

They administered the posterior pituitary extract in three different ways, namely, hypodermically, orally and by nasal insufflation of pituitary extract powder.

They made extensive studies of gastric secretion in 5 cases of active duodenal ulcers. These included repeated determinations of the volume, free and total acidity and peptic power of specimens taken during fasting and after the Ewald meal and histamine stimulation before, during and after treatment. Definite diminution of the fasting gastric secretion and slower emptying by the stomach of the Ewald meal were regular findings during treatment.

Forty-two persons with peptic ulcers were treated with pituitary preparations by Metz and Lackey, with satisfactory clinical results for 40. The duration of treatment averaged twenty-eight days, but subjective improvement was present after one to eight days. The authors advocated administering the pituitary extract by nasal insufflation of the powder, for which they devised a simple, but effective insufflator.

The Relation of Estrogenic and Anterior Pituitary-like Hormones to Peptic Ulcer.—Hurst and Stewart[33] (1929) stated:

> There is no doubt that pregnancy exerts a favorable influence on the symptoms of ulcer, especially of the stomach, and in some cases it appears to lead to actual healing, apart from any specific treatment.

Adair and Steiglitz[1] (1934) wrote:

> In twenty years at the Minnesota General Hospital no case of peptic ulcer in pregnancy had to be treated. Fortunately, patients who have had symptoms of peptic ulcer before pregnancy are usually comfortable during pregnancy, and the ulcer becomes inactive.

Others had made this same observation; among them were Sandweiss and his associates,[56] who attempted to determine the effect of sex hormones, found abundantly during pregnancy, on experimental Mann-Williamson ulcer in dogs. This ulcer develops in almost 100 per cent of dogs on whom gastrojejunostomy and anastomosis of the distal end of the duodenum to the terminal part of the ileum are done. By this method the acid chyme of the stomach is caused to come in direct contact with the mucous membrane of the jejunum, which does not receive the neutralizing secretions of the duodenum, and ulcer is produced. The first experiment of Sandweiss and his co-workers was reported as follows:

> (1) Of the 12 Mann-Williamson control dogs all died with typical jejunal ulcer within 16.1 weeks. Nine (75 per cent) died of peritonitis (following perforation) or hemorrhage. None of the ulcers showed evidence of healing.
>
> (2) Of the 15 dogs injected with theelin all developed the typical jejunal ulcers. All died within 10.6 weeks from the date of operation. Eleven (73 per cent) died of peritonitis (following perforation) or hemorrhage. None of the ulcers showed evidence of healing.
>
> (3) Of the 15 Mann-Williamson dogs treated with antuitrin-S 7 (47 per cent) died with jejunal ulcers. Four of these (27 per cent of the total) showed definite evidence of healing microscopically, *i. e.*, fibroblastic proliferation, newly formed blood vessels, a very thin pyogenic membrane, and early covering of the ulcer surface at the margin. Only 1 of the 7 (7 per cent) died of a perforated ulcer. The remaining 8 (53 per cent) showed no gross or microscopic evidence of jejunal ulcers. The dogs died of inanition as a result of the duodenal contents being diverted into the terminal ileum.
>
> Antuitrin-S, therefore, had either prevented ulcer formation, completely healed the ulcer, or caused healing to take place in 80 per cent of the Mann-Williamson dogs. Five more Mann-Williamson dogs are still alive and are being treated with antuitrin-S. One is still alive forty-one weeks post-operatively; 2, twenty-nine weeks post-operatively; 1, fourteen, and 1, six weeks post-operatively.
>
> The antuitrin-S ulcers were different than any we had previously seen. When present, they were small and superficial. There was apparent evidence of healing macroscopically. In only one instance did the ulcer perforate through all the coats. The jejunum had the appearance of being healthier than in the previous controls.

Sandweiss and his associates in their later work[57] concluded as follows: (1) Pregnancy has a beneficial effect on the symptoms of peptic ulcer. (2) Records of 70,310 consecutive hospital admissions during pregnancy showed only 1 patient with ulcer. This patient died of a perforated duodenal ulcer after stillbirth at six months. In contrast, records of 13,780 consecutive admissions of pregnant women over a ten year period showed a relatively high incidence of other gastrointestinal disorders. (3) Among 33 Mann-Williamson dogs who had daily injections of varying doses of antuitrin-S, and who died, 48.5 per cent had no ulcers and 21.2 per cent had ulcers in the process of healing. A total of 70 per cent were therefore benefited during antuitrin-S injections. Ninety-eight per cent of the control Mann-Williamson dogs died with jejunal ulcers. (4) The average survival time of the control Mann-Williamson dogs was fifty-eight days. The average for those treated by injection of anterior pituitary-like hormone was over one hundred days. Seven Mann-Williamson dogs treated by injection of APL were still living in good condition after one hundred and sixty-four to four hundred and three days. (5) In 15 patients with active symptoms of proved peptic ulcer who were treated with daily injections of 2 to 5 cubic centimeters of APL for fourteen consecutive days, the substance did not produce a greater beneficial effect than other parenteral products.

While the extract correlation between peptic ulcer and sex hormones remains to be more fully demonstrated, the findings I have listed suggest a relation.

Ziskin[62] found that estrogenic and anterior pituitary-like gonadotropic hormones are of value in the local treatment of abnormal conditions in the gingival and mucous surfaces of the mouth during pregnancy and that APL produces degenerative changes, while Sandweiss and his co-workers found that estrogenic hormone does not prevent development or stimulate healing of jejunal ulcer in dogs, but appears to accelerate perforation, and that anterior pituitary-like hormone prevents the development or accelerates the healing of these ulcers.

OTHER ENDOCRINE RELATIONS TO THE GASTROINTESTINAL TRACT

The Posterior Lobe of the Pituitary.—The manifold activities of the posterior lobe extract (pituitary solution U.S.P.; pituitrin obstetrical) are now well known, namely, their physiologic effects on the cardiovascular, respiratory and renal systems, on smooth muscle, on other glandular structures and on metabolism. These activities of posterior pituitary extract have led to definite and important clinical applications in the treatment of surgical shock, in obstetrics and in the control of diabetes insipidus.

This multiplicity of action exerted by posterior pituitary extract is obviously the combined effect of several active principles. Kamm and his co-workers[42] isolated two active principles of the posterior lobe of the pituitary, which they named "pitressin" and "pitocin." Pitressin elicits the cardiovascular, respiratory, renal, intestinal and certain metabolic effects. Pitocin is oxytocic and stimulates uterine contraction.

Pitressin given intramuscularly or subcutaneously to man stimulates both the heart and the bloodvessels by peripheral action. There are rapid blanching of the skin, a temporary fall in blood pressure and slowing of the pulse and respiration, followed after a few minutes by a rather prolonged rise in blood pressure, with moderate acceleration of the pulse and respiration. The pallor of the skin may last from one-half to one hour. The characteristic action is vasoconstriction, resulting from stimulation of the muscular tissue of the finer arterioles and capillaries. Not all vascular areas are constricted. Pitressin also stimulates the musculature of the intestines, causing rather severe cramps and urgency of defecation. This last effect has been used as the criterion of adequate dosage when pituitary extract U. S. P. has been administered to patients showing evidence of posterior pituitary insufficiency, especially that characterized by obesity. When 0.5 to 1 cubic centimeter of pituitary extract U. S. P. is injected intramuscularly or subcutaneously, marked pallor develops, accompanied by intestinal cramps which are followed by one or two bowel actions within thirty minutes. The degree of this effect, of course, depends on the functional condition of the patient's own pituitary gland. Many patients do not have these intestinal cramps until as much as 2 cubic centimeters of pituitary extract has been given. Again, in some patients in whom pituitary extract evokes these symptoms at the beginning of treatment, a tolerance for the extract later seemingly develops, and the dose must be increased 2 to 3 minims at a time until as much as 2 cubic centimeters is necessary.

It has been my experience in giving pituitary extract U. S. P. to a great number of patients over a period of years that the more evident the posterior lobe deficiency, as shown by the girdle type of obesity, the more pituitary extract is necessary to produce the physiologic result. Conversely, the less the obesity, the less is needed. Unless there is some special reason, such as labor, pituitary extract should never be given to normal or thin persons. If this is done, within a few minutes there are extreme pallor, severe precordial pain, intense intestinal cramps with urgent defecation and generalized tremulousness with occasional syncope. These patients recover within twenty to thirty minutes after they lie down. This reaction never occurs in an obese patient after the injection of 1 cubic centimeter of pituitary extract, unless perhaps when the needle enters a vein and the total dose is effective at once.

Obviously, the posterior lobe of the pituitary of a person of normal weight or a thin person is secreting sufficient posterior pituitary hormones, and the addition of more in the extract produces the exaggerated reaction described. The obese person is supposed to have hyposecretion of the posterior lobe, and the injection of pituitary extract (obstetrical) simply compensates for the deficiency of secretion. This explains why large doses of pitressin or pituitary extract (obstetrical) U. S. P. are necessary postoperatively for obese patients than for the nonobese.

Use in the Treatment of Postoperative Abdominal Distention.—Although pituitary extracts have been used from time to time in the attempt to prevent or control postoperative distention, when the two posterior pituitary principles were separated it was found that the pressor principle (pitressin) is the one which acts on the nonstriated muscle of the gastrointestinal tract and bladder. For these reasons pitressin has been found especially suitable for the control of intestinal relaxation with distention and ileus. Recently it has been used to prevent the development of distention postoperatively when the usual dose is 0.5 to 1 cubic centimeter (10 to 20 pressor units), given intramuscularly before or immediately after operation; subsequent injections of the same dose may be given at four hour intervals for 10 or 12 doses; in cases of complicating peritonitis pitressin medication may be continued for a week or longer.

Elimination of Gas Pockets.—Roentgenograms of the spine and pelvis, of the gallbladder and of the kidneys, ureters and bladder are frequently rendered worthless by shadows of gas pockets in the intestine. Administration of pitressin is of great value in eliminating this troublesome factor. The suggested treatment is the intramuscular injection of 1 ampoule of pitressin at 6 A.M. Another injection is made at 8 A.M. Roentgen study may be begun at 8:30 A.M. If the patient is thin, 0.5 cubic centimeters may be used for the first dose, and if no untoward effect is produced, 1 cubic centimeter may be given at the second injection.

Effect of Metabolism.—It is necessary to consider the liver and the pancreas, for they develop in embryonic life as appendages in conjunction with the gastrointestinal tract in the region of the duodenum.

Metabolism of Fats—Bailey and Bremer[2] and Camus and Roussy[9] have attributed no importance to the hypophysis in the physiologic regulation of fat metabolism and the development of obesity, because the symptoms frequently ascribed to pathologic changes in the hypophysis can be fully reproduced by experimental injury of the base of the midbrain and especially of the tuber cinereum.

Raab,[54] experimenting with dogs, came to the conclusion that the hypothalamus contains the fat-regulating center. Destruction of the tuber cinereum or severance of the nerve pathways between the hypothalamus and the liver in dogs results in a marked increase in the circulating neutral fat which ordinarily is absorbed and metabolized by the liver. Raab also showed the dependence of the fat-regulating center in the hypothalamus on a normal supply of pituitrin. The subcutaneous injection of several cubic centimeters of pituitrin caused the complete disappearance of the neutral fat from the blood. One-tenth of the subcutaneous dose of pituitrin injected into the brain ventricles produced the same effect. If, however, the tuber cinereum is mechanically destroyed, of if the nerve pathways between the tuber cinereum and the liver are severed, then the injection of pituitrin has no effect on the reduction of the circulating neutral fat.

Raab concluded:

> Pituitrin promotes the absorption and destruction of circulating fat by the liver through nervous pathways, starting in the tuber cinereum and running through the cervical spinal cord and the abdominal splanchnic to the liver. Any disturbance of the coöperative pituitary-mesencephalic system would lead to a retention of excess fat amounts in the body and thus lead to obesity.

The Anterior Lobe of the Pituitary.—Collip[12] stated:

> That the pituitary hormones are not essential for the functioning of the gastrointestinal tract is shown by the failure of hypophysectomy to produce any well defined changes in the digestive functions.

This statement is probably correct, providing the liver and pancreas are not considered as accessory organs of the gastrointestinal tract.

Normal function of the gastrointestinal tract (digestion) depends, besides other factors, on normal hepatic pancreatic function, and these are markedly influenced by normal or abnormal pituitary function.

With hyperfunction of the anterior lobe of the pituitary in adult life, acromegaly is produced, which is characterized by overgrowth of all the tissues of the body, including those of the gastrointestinal tract, which condition is known as splanchnomegaly. In pituitary cachexia (Simmonds' disease) there is hypofunction or afunction of the anterior lobe, characterized by a clinical picture of generalized atrophy. Among the symptoms are anorexia and extreme emaciation.

Glycosuria with acromegaly and the increased sugar tolerance in the presence of hypopituitary conditions were noted by Goetsch, Cushing and Jacobson,[26] and amply confirmed, suggesting that the pituitary gland has some endocrine relation to the function of the pancreatic islets.

Houssay and Magenta in 1924 announced that hypophysectomized dogs have a markedly increased sensitiveness to insulin. Houssay and Biasotti[32] in 1931 reported that the symptoms of diabetes in depancreatized dogs were either cured or greatly relieved by hypophysectomy, and that if anterior pituitary transplants were made into these depancreatectomized, hypophysectomized dogs, the diabetes was made worse. This work was confirmed by Barnes and Regan.[3] Although completely depancreatized dogs are totally diabetic and will die shortly if not treated with insulin, when these dogs are hypophysectomized, they have been known to live for from six to nine months without insulin treatment.

In 1932 Evans and his co-workers[20] announced the production of hyperglycemia and glycosuria in normal animals by injection of anterior pituitary extracts.

The Thyroid.—The thyroid gland, by virtue of its internal secretion, influences the cellular metabolism of the body and in this way may have a direct affect on the gastrointestinal tract; that it has a specific action in the digestive processes has not been indicated.

In hypothyroidism with decreased cellular activity, there is a generalized slowing of the body functions, reflected in the gastrointestinal tract by anorexia and constipation. There is usually an increased sugar tolerance.

Hyperthyroidism is accompanied by increased cellular metabolism and acceleration of body functions beyond their normal rate. The catabolic processes exceed the anabolic, thereby necessitating an increased food intake, accompanied by increased appetite.

Thyroid crisis is characterized by extreme toxemia, hypercombustion and overwhelming excitation of the circulatory and nervous systems, psychosis and gastrointestinal upsets of vomiting and diarrhea. Patients with hyperthyroidism, especially those in whom the condition is of comparatively long duration, frequently have acute indigestion and diarrhea, which may be intractable for two to three days. The ordinary medicaments for diarrhea are usually of no avail, and the condition ends rather abruptly when treatment is administered to quiet the nervous reactions.

Robinson 55 stated that goiter and gastroduodenal ulcer seldom occur in the same person, but in an analysis of the protocols of 2,000 routine postmortem examinations in which a complete survey of the gastrointestinal tract was made, Robertson and Hargis (1925) pointed out the frequency with which patients dying of thyroid disease, particularly those with hyperthyroidism, show evidence of gastric or duodenal ulcer. Neidhardt and Blaum[53] (1937) reported the presence of 7 duodenal ulcers and 1 pyloric ulcer among 40 patients, 37 of whom had exophthalmic goiter and 3 thyrotoxicosis. They attributed the high incidence of ulcer in these goitrous persons to hyperirritability of the vegetative nervous system.

Sugar tolerance is usually decreased, with a consequent hyperglycemia.

The Pancreas.—Since the pancreas and liver will be discussed at length in other chapters, only certain hormonal relations with the gastrointestinal tract will be considered here.

The fascinating story of the isolation of insulin from the pancreatic islets is too well known to permit discussion in this chapter. The possibility that "incretin" stimulates the pancreatic islets to secrete insulin indicates another interesting relation between the pancreas and the gastrointestinal tract.

After the isolation of insulin by Best and Banting,[5] Fisher[24] and others discovered that completely depancreatized dogs adequately treated with insulin usually do not survive more than two or three months. The most obvious change found after death was an extensive fatty infiltration and degeneration of the liver. In one experiment Fisher noted extreme atheroma of the aorta. McLeod and his associates found that the addition of raw pancreas to the diet prevented the development of these liver changes and extended the survival period of these dogs. The addition of 10 Gm. of lecithin daily to the diet of depancreatized dogs treated with insulin also prevents the liver damage and extends the survival period.[30] Choline is the active constituent of lecithin which produces this effect.[6] A long series of experiments was done by various investigators to rule out the possibility that the pancreatic secretion might contain the preventive agent.

It was found that a dose of 2 Gm. of choline daily (but not less) will prevent or relieve fatty liver in depancreatized dogs. It was also found that 25 Gm. of fresh pancreas is equally effective in relieving the condition. However, the amount of choline contained in 25 Gm. of fresh pancreas is thirty times less than the effective dose of choline alone.

A fat-free alcoholic extract of beef pancreas, when fed to depancreatized dogs, proved as effective orally as either raw pancreas, lecithin or choline and is considered to be a fat-metabolizing hormone concerned in the normal transport and utilization of fat.[16]

Dragstedt[15] concluded as follows:

> The facts that have appeared as a result of this study seem to warrant the conclusion that there is present in fresh pancreas and probably in the islet tissue a specific substance, apart from insulin, which plays a role in the transport or utilization of fat. Since it is not present in the external secretion of the pancreas, it is probably an internal secretion or hormone, for which we have chosen the name "lipocaic." This is derived from the Greek and suggests in a general way the oxidation of fat.
>
> The function of this hormone is still, however, very little understood.

The Adrenal Glands.—The relation of the adrenal glands to the gastrointestinal tract was considered in part under the section relating to the autonomic nervous system. The neuromuscular mechanism of the entire gastrointestinal tract is responsive to epinephrine, sympathin and acetylcholine, and the motor and secretory activity are markedly influenced by these active principles.

The influence of epinephrine and sympathetic stimulation on the digestive and motor activity of the stomach and intestines during periods of emotional stress, such as fright, fear and anger, has been referred to. A common complaint of many persons is functional indigestion, which in numerous instances results from long-continued nervous tension, such as is produced by worry, unhappiness, financial difficulties and over-work. This nervous interference with the digestive processes may manifest itself clinically by hyperacidity, distention, eructation, pyrosis and occasionally pylorospasm. The nervous "high tension" type of person is said to be more subject to the development of ulcer than the calm, phlegmatic type. Also, ulcer in the process of healing frequently relapses as the result of emotional shock or other nervous stimuli.

Carbohydrate metabolism is greatly disturbed by complete adrenalectomy. Verzar and Laszt[60] noted an inhibition of dextrose absorption from the intestine of the adrenalectomized rat. Whereas in the normal animal dextrose is absorbed much more rapidly than other forms of sugar, this preferential absorption is so impaired by adrenalectomy that a fairly large dose of 50 per cent dextrose solution is no longer tolerated, and death occurs from profuse watery diarrhea associated with a high blood viscosity. The previous administration of cortin prevents death, and Verzar and Laszt suggested that this substance could be utilized as a means of assay. Malabsorption of dextrose may be due to impaired ester formation, since dextrose is said to be attached to an acid, possibly flavine phosphoric acid, during absorption.

Verzar and Laszt explained the passage of water and sodium from the blood of the rat into the intestine in part or wholly by defective carbohydrate absorption secondary to disordered flavine phosphoric acid synthesis, similar osmotic disturbances accounting for other phenomena. Against this, American observers have stated that loss of blood sodium precedes all gastric and intestinal disturbances in the dog.

An equally striking disturbance of fat absorption in the rat has been ascribed to a similar inability of free intestinal fatty acids to recombine in the epithelium to form esters. Both fat and carbohydrate metabolism can be restored to normal by the injection of cortin.

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CHAPTER XLVI

GASTROINTESTINAL MANIFESTATIONS OF ARTHRITIS, GOUT AND DIABETES

ARTHRITIS

There are several types of arthritis, but here only the two types encountered most frequently, namely, the atrophic, or infectious, type, and the hypertrophic, classified as metabolic or senescent, will be considered. Before attention was directed to focal infection as a cause of the infectious, or atrophic, type, much attention was given to hereditary factors, physique, food intake, etc. With the enthusiastic acceptance of focal infection as a cause of infectious arthritis, many of these basic factors were entirely forgotten for a time. Hench's[24] excellent discussion summarized the evidence and indicated that infection with streptococci, as of 1935, may well be accepted as the cause of atrophic arthritis. In 1938 Cecil and Angevine,[11] in an analysis of 200 instances of infectious arthritis, concluded that "the time has arrived for a complete revaluation of the focal infection theory. Undoubtedly there are cases of infectious arthritis which result from focal infection. It would appear from this study that chronic focal infection plays a relatively unimportant role." More recent work indicates that several groups of workers, including Boots and his associates, have established that serum from patients with infectious arthritis agglutinates strains of hemolytic streptococci to a high titer. However, they expressed the opinion that the relation of hemolytic streptococci to the etiology of infectious arthritis is not definitely established. Oldershaw,[47] an English student of rheumatism, stated that infection is the cause of atrophic arthritis. Important factors are the severity of infection, casual organism, the amount of toxic absorption and, above all, the reaction of the patient's tissues to the toxin present.

Hypertrophic (senescent) arthritis is a different type of joint disturbance. Its etiology is also debatable. Llewellyn[37] expressed the opinion that "future research will show that all varieties of osteoarthritis hark back to similar etiological factors." This statement includes the menopausal type, in which endocrine factors are thought to play an important role.

The importance of the gastrointestinal tract in causation of infectious arthritis and its place in the management of patients with this condition have received recent added emphasis. Pemberton[48] expressed the belief that the gastrointestinal tract in arthritic patients is subject to dysfunction:

> This may express itself in the form of flatulence, dyspepsia, costiveness, coated tongue, hypoacidity or achylia, and the general condition is one of atony of muscular structure and usually disturbed function of the mucosa as well.

He stated further that in the later stages of infectious arthritis these changes are invariably present.

Pemberton[49] has published studies indicating that

> the synovial fluid of joints is in surprisingly close communication with the circulating blood and also with the gastrointestinal tract. . . . It is now known that if

glucose be ingested by mouth it will appear in the joint fluids with surprising rapidity, reaching there concentrations in excess of those in the blood. It is also known that other substances may reach the joint cavity from the gastrointestinal tract and quite obviously there must be considered the possibility of the entry into the joint of substances having a detrimental as well as a beneficial effect.

Changes in the colon, as determined by *x*-ray studies, have been found by Pemberton in a large percentage of his patients. Burt and his associates,[9] of England, recorded 28 instances of chronic infectious arthritis in which careful barium enema studies were made. Of these, in 18, or 64 per cent, the colon was entirely normal. In 10, there was some significant dilatation of some part of the colon. No case of spastic colon was observed. Any departure from the normal was from the sympathetic rather than the vagal side.

Among those who hold the idea of the causative role of intestinal intoxication untenable is Keefer.[31] He found no constant or consistent deviation from the normal through the medium of *x*-ray studies of the gastrointestinal tract of patients with arthritis and, impressively, no pathologic alteration in the intestines of these patients at death.

The possible relation between gastric secretion and arthritis has been repeatedly studied. The results are similar and are well illustrated by the findings of Moltke and Ohlsen,[44] of London. They gave histamine (0.5 mg.) to 69 patients with chronic infectious arthritis and recorded the fractional findings for acid. Thirty-six per cent showed histamine-refractory achlorhydria. The authors concluded that the high incidence among patients with true rheumatic arthritis cannot be explained on the basis of what is known about patients in the same age groups, or as a result of age or duration of disease. Achlorhydria does not seem to be associated with any subgroup of true rheumatic arthritis.

Dr. Jessie Ogilvie[46] gave Ewald meals to 60 healthy children and to 100 children convalescing from acute inflammatory rheumatism. While this is a different type of infection, the results are interesting. Twelve per cent of her convalescent patients and 5 per cent of the normal children used as controls were found to have lowered or no acid, but 24 per cent of the rheumatic children and 13 per cent of the normal had hyperacidity. The blood $p\mathrm{H}$ was unchanged in all groups. Low or absent acid in 12 per cent of her convalescent patients is a striking finding. However, a relation to acute rheumatic fever was not proved.

Moltke and Ohlsen,[44] in a series of normal adults in different age groups, found that 40 per cent of those forty to forty-nine years of age, 27.9 per cent of those fifty to fifty-nine and 28 per cent of those sixty years of age or older had achlorhydria.

Keefer and Bloomfield[32] studied 94 patients with all types of arthritis; 18.4 per cent showed anacidity. The Ewald test only was used here, however. These authors found no higher incidence in this group than in a control group of the same age and sex.

The significance of achlorhydria and achylia in relation to the causation of infectious arthritis is not clear to me as it appears to be to some of the authors I have cited. In the first place, these changes occur about as frequently in persons of the same age who do not have arthritis. Secondly, while diminution or absence of acid theoretically permits bacteria to live in the stomach and to pass on into the intestine, bacteria in the small bowel may still not be an etiologic factor in arthritis. To me, a more substantial contention seems to lie in a possible relation between diminution or absence of acid and the deficiency diseases.

Greenberg, Rinehart and Phatak[20] suggested that vitamin C deficiency may be an important contributory mechanism in the cause of atrophic arthritis in "some cases." Chemical determination of vitamin C in blood plasma, body tissues and urine has demonstrated low levels with chronic infectious arthritis.[18] Experimental giving of adequate amounts of vitamin C to patients with chronic infectious arthritis indicates that a deficiency of vitamin C may exist in the presence of adequate intake.

Rowlands[58] and Fletcher and Graham[19] have indirectly related vitamin B to chronic infectious arthritis, noting atony of the musculature of the colon frequently. Fletcher and Graham gave vitamin B in liberal amounts and noted improvement in the tone of the bowel, accompanied often by clinical improvement. Experimentally, a diet deficient in vitamin B_2 has resulted in degenerative alterations in the gastrointestinal tract.[42]

Vitamin deficiencies are likely to be multiple. Three factors may be operative: (1) a limited vitamin intake as a result of loss of appetite, etc.; (2) failure of absorption of adequate amounts of vitamins, owing to gastrointestinal disturbance, and (3) chemical alteration or destruction of vitamin complexes within the intestinal tract, owing to gastrointestinal abnormality.

McCarrison[39] has shown that defective nutrition may cause widespread changes in the gastrointestinal tract. Such changes can interfere with absorption. Other factors may also alter absorption, such as the composition of the intestinal contents, motor and secretory disturbances and many others, internal and external.

Recent experimental work by Elizabeth Robertson[55] has shown that diets deficient in minerals (calcium and potassium) fed to rats for four weeks produced interesting changes. The walls of the lower part of the intestines were thinner. The weight of the lower part of the intestines with their contents was greater. Intestinal stasis, with slow elimination, was marked. Smaller amounts of feces were excreted; considerably greater numbers of bacteria were present in the cecum, and the nitrogen in the intestinal content was increased. This suggests a poorer absorption of protein.

A group of 19 children were placed on a diet low in calcium and potassium for four weeks. Seventy-four per cent of these children became constipated. The constipation was relieved when calcium alone was returned to the diet.

The lack of other nutritional substances, such as vitamins A and C, also can induce degenerative changes in the gastrointestinal tract.[43] Infection has been shown to interfere with the metabolism of vitamin C and to decrease the absorption of this nutritional substance. Damage to organs such as the liver can prevent storage of vitamin A and disturb the metabolism of vitamin D. The lack of vitamin D is known to interfere with the absorption of calcium. Race[53] recorded that evidence so far adduced in the study of various chronic rheumatic diseases, especially of chronic infectious arthritis, demonstrates that the amount of carotenoid pigments and vitamin A in the serum are subnormal, and that a similar condition obtained as regards vitamin C.

Dryer and Reed[14] treated a series of 67 patients suffering from various types of arthritis with large doses of vitamin D, with improvement in 66 per cent after periods varying from one week to six months. However, the authors did not call these disturbances vitamin D deficiency diseases.

It may well be that the changes in the gastrointestinal tract, as recorded by Pemberton and others, will be found to have an etiologic relation to chronic arthritis of both types, atrophic and hypertrophic, linked up with vitamins. That prophylactic and therapeutic studies on the effect of vitamin C, for example, on chronic arthritis have so far been abortive is not disheartening. An abundant field for further work in this direction remains.

On the etiologic relations of allergy, particularly as concerns the gastrointestinal tract, to arthritis there is a wide diversity of opinion. Gudzent[21] since 1926 has repeatedly expressed the opinion that rheumatism is an allergic response to protein. Rossle, [56] of Berlin, has been less emphatic in this contention. Aschoff,[2] on the other hand, summarized the opinion of the majority of students on this subject, both in England and on the continent, as follows: "We arrive, therefore, at the result that the allergic phase plays no part either in osteoarthritis (hypertrophic arthritis), which involves essentially mechanical or metabolic factors in the widest sense, or in rheumatoid conditions (chronic infectious arthritis) arising from specific or non-specific infections."

In America, Pottenger 51 found gastrointestional symptoms considered due to food allergy in 94 of 100 patients with atrophic and hypertrophic arthritis. In 88 of this group "the presence of food allergy was proved by the precipitation of their gastrointestinal symptoms by the addition of offending foods and the relief of symptoms by the subsequent removal of the foods." He expressed the further opinion that in these instances food allergy is not the only disturbance present in the gastrointestinal tract, but appears to be conditioned by other abdominal pathologic processes. He concluded that gastrointestinal symptoms of arthritis have no definite pattern.

Rowe[57] expressed the opinion that gastrointestinal food allergy is a common and often overlooked cause of "many mild and obscure as well as moderate and severe symptoms of this type." Elimination diets, which he originated, occupy an important place in detection of the offending foods.

In contrast to these reports, Hench[23] called allergic factors unimportant. Wilmer and Miller[69] reported that allergic reactions following the ingestion of food are not unusual, but that they occur most often in some other mucous membrane surface, or the skin, rather than in the mucosa of the gastrointestinal tract. Occasionally only have they found gastrointestinal conditions that so closely follow the ingestion of food to which the patient is sensitive that they must be described as allergic. They expressed the belief that in some instances acute gastritis or gastroenteritis, colitis (particularly mucous colitis), gastric and duodenal ulcer and possibly gastrointestinal allergy are due to a hypersensitivity to specific foods. They recorded three instances of severe gastrointestinal pain due to food allergy. In a large percentage of instances of gastrointestinal allergy, sigmoidoscopic examination of the lower part of the bowel showed the same picture as that of nasal allergy, a pale, pearly, thick, boggy, edematous mucous membrane, over the surface of which is a thick gelatinous secretion. Complete chemical studies of the blood in their patients with gastrointestinal allergy showed no significant change. In a few instances acute abdominal pain, by a process of exclusion, was thought to be an allergic response and was entirely relieved by injection of epinephrine.

Table 37.—Gastrointestinal Manifestations in Patients With Atrophic and Hypertrophic Arthritis and in Normal Persons, 100 Each Group

Age decade		11–20	21–30	31–40	41–50	51–60	61–70	71–80	81–90	Total per cent
Epig. pain	Atrophic	1				3		1		3
	Control					2				2
	Hypertrophic			1		1	1	1		4
Epig. dis.	Atrophic	1	1	3	4	9	2	2		22
	Control			2	8	7	5	1		23
	Hypertrophic		1	1	1	2	10	3		18
Belching	Atrophic			7	1	7	2	2		19
	Control			2		6	2	1		11
	Hypertrophic		1	1		3	6	2		13
Ht. burn	Atrophic			1		1	2			4
	Control			1			1			2
	Hypertrophic					1	1			2
Fulness	Atrophic			2		2	3	2		9
	Control		1		2	5	1			9
	Hypertrophic					4	1	1		6
Anorexia	Atrophic				3	1	1			5
	Control				1	1				2
	Hypertrophic			1		1		3		5
Nausea	Atrophic		1	2	3	2	1	1		10
	Control		2	2	2	4				10
	Hypertrophic					4				4
Vomiting	Atrophic				2	1	1			4
	Control		1	2	2	1				6
	Hypertrophic				1	1	1			3
Cost.	Atrophic		2	6	8	11	9	5		41
	Control		2	9	6	10	9	1		37
	Hypertrophic		1	2	3	5	8	5	1	25
Abd. pain	Atrophic			2	2	3	1	1		9
	Control		1	2	4	3	1			11
	Hypertrophic				2	3	1			6
Diarrhea	Atrophic				3	1	1			5
	Control		1	1	3	1	1			7
	Hypertrophic			1	1	2	1			5

In my own material, atrophic arthritis was recorded as a medical diagnosis in 381 of a total of 8,600 cases. Hypertrophic arthritis was recorded in 223 of this same number. For 100 patients taken at random from each of the aforementioned groups and a control group of 100 persons of the same age decades who were found, after study and examination, to have minor ailments only, I have charted the gastrointestinal manifestations. Group 1, Table 37, consisted of patients with atrophic arthritis; group 2, controls, and group 3, patients with hypertrophic or metabolic arthritis. The decades of life in which these symptoms occurred in the three groups were much the same. There was no significant difference in the number in which epigastric pain, epigastric distress, heartburn, vomiting and abdominal pain were complained of. In the group with atrophic arthritis, belching was recorded in 19 per cent, as compared with 11 per cent of the controls and 13 per cent of the group with hypertrophic arthritis. "Fulness" occurred in only 2 per cent of those with atrophic arthritis, as compared with 9 per cent in each of the other two groups. Anorexia occurred in 13 per cent of group 1, 5 per cent of group 2 and 2 per cent of group 3.

Nausea was present in 10 per cent of groups 1 and 2 and in only 4 per cent of group 3. Constipation was complained of by 41 per cent of group 1, 37 per cent of group 2 and 25 per cent of group 3. Diarrhea was recorded in 5 per cent of group 1, 1 per cent of group 2 and 4 per cent of group 3.

From these data it is evident that diarrhea occurred about equally in the groups with arthritis and more often in them than in the control group. Further study showed that parasitic infestation of the bowel and ulcerative colitis were not responsible for the diarrhea.

Constipation occurred about equally in the first and second groups and decidedly less often in the third group. Anorexia occurred much more often with atrophic than with hypertrophic arthritis. "Fulness" was present in many less cases of atrophic than of hypertrophic arthritis. Belching was more frequent with atrophic than with hypertrophic disease.

Physical examination revealed focal infection in 60 per cent of the first, 37 per cent of the second and 39 per cent of the third group. The enthusiasm with which infection was searched for seemed to me to be about the same in each group.

A history of hives, eczema, asthma or hay fever, suggesting an allergic background, or a positive skin test with pollen or food was found in 18 per cent of the first, 3 per cent of the second and 6 per cent of the third group.

Endocrine imbalance, largely hypothyroidism, was evident in 36 per cent of the first, 26 per cent of the second and 31 per cent of the third group.

Secondary anemia (the hemoglobin concentration being 75 per cent or lower with the Dare apparatus) was present in 25 per cent of the first, 26 per cent of the second and 9 per cent of the third group.

Symptomatic treatment is capable of relieving a majority of these complaints and of correcting the anemia and the endocrine imbalance. Hypoacidity or achylia, if present, may be corrected by the exhibition of dilute hydrochloric acid or by the use of sour fruit juices, to be detailed in the discussion of the management of gout.

Constipation should be corrected by dietary measures and the use of retention oil enemas. Its relief is often of distinct benefit to the arthritis. Diarrhea, much less frequently encountered, should be relieved.

The increasing interest in the use of gold salts in the treatment of infectious arthritis calls for a word of comment. It is not as yet known in what manner gold salts act beneficially in some instances of infectious arthritis. That they do is definitely established. There are hazards in treatment by this means, and before it is attempted one should familiarize himself thoroughly with the type of patient in whom improvement may be expected from this procedure, that is, the patient with an active inflammatory stage of infectious arthritis. Possible toxic reactions may follow some months after this type of therapy has been discontinued. Steinbrocker[59] has written specifically about the entire problem of the use of gold in the treatment of arthritis.

The deficiency diseases and vitamin disturbance occupy an important place in the study and management of arthritis and deserve special emphasis.

In conclusion, the abnormalities of the gastrointestinal tract, emphasized particularly by Pemberton,[50] indicate the importance of this tract in the management of the arthritic person. I believe that this tract not infrequently contributes materially to arthritis, and further that the dietetic management of the arthritic patient is not to be overlooked. It might even be said that a proper handling of the gastrointestinal tract of an arthritic patient may in some cases be the most important factor in successful management.

GOUT

"Tollere Nodosam Nescit Medicina Podagram"
(Medicine Cannot Cure the Knotty Gout)

Gout apparently is not recognized as frequently as it should be at the present time. Hench[27] found that only 12 of 100 patients with this disease had had a correct diagnosis before admission to the Mayo Clinic, where its incidence is about 2 per 1,000 admissions. Among my own office patients, 16 of a total of 8,600 were found to have this disease, an incidence of 0.18 per cent.

The cause of gout is still unknown. However, accumulated evidence indicates that it is neither an infectious nor a deficiency disease, but a metabolic dyscrasia.[60] Edgecomb[16] defined gout as "a disorder of nuclein metabolism resulting from the imperfect oxidation of the purine bodies and in the retention of uric acid in the blood and tissues." According to Wells,[65] the attempt to explain gouty metabolism as a result of enzymatic abnormalities fails because recent studies have not located anywhere in the body an enzyme destruction of uric acid. Viewing gout clinically "and more particularly the hypersensitiveness of its victims to the most varied stimuli, dietetic and otherwise, one inclines rather to an inherent instability of nuclein metabolism."[65] "An indiscretion in diet, a trivial injury, a disturbed intestinal flora may be followed by a general disturbance of nuclein metabolism."[22]

The intimate relation between the gastrointestinal tract and gout has been thoroughly established. Commonly acute attacks of gout are preceded by or associated with flatulence, heartburn, anorexia, scanty urine and constipation. Exacerbations or relapses commonly follow symptoms of gastrointestinal or hepatic dysfunction. A carefully taken history of a person with gout frequently reveals an onset of acute symptoms, characteristic of which is pain in either great toe, following almost immediately on excessive indulgence at table. Any form or article of food which interferes with digestion has been shown to incite an acute attack.[61] Excess of starchy foods appears to induce attacks in the subjects of amylaceous dyspepsia, and acute gout is as often initiated by the ingestion of too much food of all kinds as by the eating of too much meat. Duckworth[15] summarized the matter succinctly as follows: "The way to avoid gout is to avoid second helpings." Even excess of fat in the diet has been shown by Lockie and Hubbard[38] to increase uricemia and provoke more numerous attacks, both of which may be reduced by placing the susceptible person on a diet composed largely of carbohydrate.

I have been unable to find a report on the presence or absence of acid in the stomachs of gouty persons. Bloomfield and Polland,[5] in an extensive review of the subject of anacidity accompanying various clinical disorders, did not mention gout. Since anacidity occurs in approximately 20 to 40 per cent of otherwise normal persons, it is not unlikely that about that percentage of persons with gout lack free acid. Hyperacidity is sometimes present,[36] but its precise incidence with gout I am unable to ascertain.

Absence of free hydrochloric acid in the stomach may permit the presence of bacteria in the stomach, which may act as a disturbing factor. Further, the absence of acid undoubtedly allows the passage of protein food into the intestine in a poor state of digestion. Hyperacidity acts in a disturbing manner by secondarily intensifying intestinal indigestion, since acid chyme antagonizes the activity of the pancreatic enzymes. These are: trypsin, a powerful proteolytic enzyme which acts best in an alkaline medium with a pH between 8 and 9; amylase, a starch digestant acting most effectively at a pH of 6.7 to 7, and lipase, which splits the fat molecule into fatty acids and glycerin. The emulsifying action of this enzyme, an important step in the digestion of fat, takes place almost entirely in the small intestine and occurs only in an alkaline medium.[4]

The disturbed metabolism of uric acid with gout has received much attention. Normal blood contains up to 3 mg. of uric acid per 100 cubic centimeters. During an acute attack of gout, the concentration of uric acid may reach 10 mg. Uric acid in the blood comes from two sources, the purine bases in the food and those in the body. The purine bases come, in turn, from the nucleoproteids of the cell nuclei. Uric acid is found in the feces of fasting persons, an observation confirmed many times.[40] Muscle activity forms uric acid, but there is no positive information that uric acid is formed by any of the cells of the digestive tract.

The increase of uric acid in the blood is explained by (1) increased formation, (2) diminished destruction and (3) lessened excretion. The only definite evidence of increased formation of this substance in the body with gout is the recent report published by Talbott and Coombs.[60] Diminished destruction of uric acid has been suggested by Brugsch,[8] but it is doubtful if this is important. Reduced excretion of uric acid accompanying this condition is the explanation most frequently championed. In this connection, nephritis must be eliminated as a complicating factor, since nitrogen retention occurs early in this disturbance and uric acid is a nitrogenous substance. The excretion of uric acid with a purine-free diet and after a meal rich in nucleoprotein is much less for the gouty than for the normal subject.[4] Lessened excretion of uric acid especially notable before an acute episode. The excretion of uric acid gradually increases for a few days after the beginning of an attack and then returns to normal.

Volini[62] expressed the belief that a functional disturbance of the kidney effects a lessened uric acid excretion in the presence of this condition. There is no agreement as to the effect of nucleins in the diet on excretion of uric acid. Since digestive disturbances are marked in gouty persons the difference may be due to variation in absorption, or the purine may be destroyed before absorption.

In line with the possibility that decreased elimination of uric acid may be a factor in gout is the presence of the characteristic tophi in gouty persons. Tophi are composed of deposits of crystals of the sodium salt of uric acid, sodium urate. These deposits occur in cartilaginous tissue in such locations as the great toes, the fingers and the ears, at times in the soft tissues and late in the disease in the bones. Christian[12] has summarized the diagnostic criteria of gout as follows: "We are not warranted in making a diagnosis of gout at present unless we get positive evidence of urates somewhere in the body, tophi, or a very marked disturbance of uric acid metabolism, the main feature being its accumulation in the blood in a patient in whom there is no evidence of a defective renal lesion." Hench,[25] however, found normal or lower figures for this substance in 28 of 100 proved instances of gout.

Whatever the role of an increased amount of uric acid in the blood stream in the acute attack of gout, disturbed intestinal function is intimately related to it. Intestinal derangement may be brought about in several ways: too little or too much hydrochloric acid entering the small bowel from the stomach; deficient amounts of pancreatic enzymes; diminished secretion of the intestinal juice (succus entericus); deficient intestinal motility, and, in susceptible persons, ingestion of improper food or of too large amounts of food. The presence of bacteria in the small intestine, as a result of or coincident with disturbed digestion by the small bowel, may further alter the digestive processes of this important tube. "The gastrointestinal defects, secretory or motor, which chequer the course of gout, enhance the pathologic activity of the intestinal flora and incidentally the liability to infection at various sites in the intestinal tract."[36]

The treatment of gout, which over the past one hundred years has laid emphasis on the importance of the gastrointestinal tract, stresses diet, the elimination of alcoholic beverages and, more recently, the ingestion of vitamins and minerals. The acute attack responds well to rest in bed, warmth, a purine-free diet of fruits, cooked vegetables, bread, milk and eggs and the drugs cinchophen and neocinchophen in 5 grain doses four to five times daily for a four day period. The possibility of toxic liver damage from these drugs must be borne in mind and their use carefully supervised. Colchicum, either the tincture or the wine, has long been used. More recently the crystalline form has been advised.[13] It may be given in doses of $\frac{1}{120}$ grain each two hours until 14 doses have been given. Diarrhea, nausea and vomiting indicate its withdrawal for the time being.

The treatment of gout in the interval between acute attacks is again a matter of diet, alcoholic restriction and, as advocated more recently, the intermittent use of colchicine, $\frac{1}{120}$ grain three times a day for two or three days of each week. The routine use of cinchophen in the treatment of gout has been championed by Hench,[26] who contended that cinchophen should be used three consecutive days a week, but not on the other days; that the patients should take alkali and large amounts of fluid and sweetened fruit juices daily, and that if this procedure is followed the danger of a toxic reaction in a person taking this drug is about 1 in 500,000, which he described as "negligible." Limitation of the purine-containing foods, such as kidneys, sweetbreads, liver and beef, is advisable. Lamb, game and chicken should be taken in moderation. Any form or article of food, whether protein, starch or fat, which is known in the individual instance to disturb digestion should be avoided altogether. Acute attacks of gout are often induced by the consumption of too much food.

It is a safe plan to avoid all forms of alcohol. Wines and spirits probably condition the patient to gout on account of their alcoholic content. They stimulate the appetite and may lead to over-eating and may have an irritant action on the gastrointestinal mucous membrane, interfering with normal digestion. Coffee should be taken in moderate amounts or omitted altogether. Weak tea is permissible.

The absence of free hydrochloric acid in the stomach calls for the exhibition of 18 minims of tenth normal hydrochloric acid in a full glass of water with each meal. It is best taken through a glass tube. As a substitute for dilute hydrochloric acid, the juice of a large lemon in a glass of water or 4 ounces of grapefruit juice will be found very efficient. Just how these sour fruit juices help is not certain. It has been suggested that their organic acid content is the *modus operandi.* Carlson[10] has offered the explanation that sour fruit juices stimulate an increased flow of pancreatic enzymes.

Chronic disease of the gallbladder or biliary tract or lessened bile formation by the liver—in a word, a reduction in biliary secretion—is an important complicating factor in gout. A normal flow of bile is essential to the maintenance of several physiologic processes. These include aid to the digestion and absorption of fats, acceleration of the action of pancreatic enzymes, facilitation of the digestion of nucleoproteins and promotion of normal intestinal motility. "Like the kidney, the bile plays an important though generally forgotten role in regulating the acid-base and calcium balance in the blood."[66] Thus, disease of the biliary tract calls for attention. Gallbladder drainage by the Meltzer-Lyon technic may be helpful. The use of cholagogs to stimulate emptying of the gallbladder and extrahepatic ducts or of a choleretic agent such as crystalline dehydrocholic acid to stimulate the action of the secretory cells of the liver may likewise serve a useful purpose.

DIABETES

The literature emphasizing the relation between the clinical entity known as diabetes and the gastrointestinal tract has increased markedly since the first edition of this book. This can be grasped by reviewing a recent book by Lagerlöf,[35] in which the intricacies of many problems of digestion are discussed in detail. The chapters dealing with the newer phases of the physiology of digestion and of the interrelation of gallbladder, gall duct and pancreatic disease and their association with diabetes are comprehensive.

Diabetes is a metabolic disorder due to an insufficient supply of a pancreatic hormone, insulin. There are a lowered store of dextrose in the liver and an increase in the amount of sugar in the blood and in the urine.

Joslin[29] estimated that 2 per cent of the entire population of the United States or "approximately 2,500,000 have or *will have* the disease before they die."

Diabetes is intimately concerned with the liver, both as a storehouse for glycogen and as the organ in which aminoacids from the digestive tract and aminoacids derived from the breakdown of proteins in the body are converted into glycogen. Diabetes is likewise linked up with the pancreas, the organ which elaborates the hormone insulin, and with the gastrointestinal tract, from which the carbohydrates and the proteins (58 per cent of which are converted into sugar) are taken up by the blood stream after a series of chemical changes known under the general term digestion. Since the liver, pancreas, stomach and small and large bowel constitute a major portion of the gastrointestinal tract, the intimate relation of that tract to diabetes is evident.

This review of the gastrointestinal manifestations of diabetes may well begin with the mouth. Kent[33] found that the patient with diabetes is more subject to tartar formation that the nondiabetic person and that there is a high incidence of gingivitis. Williams[68] reported an unusual type of pyorrhea among a group of 138 diabetic patients studied by him. To maintain good teeth, the diet must be adequate in vitamins and minerals, and the diabetes must be controlled.

The liver is assuming increasing importance in the study of diabetes. One function of insulin is assistance in the change of dextrose into glycogen. This occurs in the liver, which is a most important storehouse for glycogen, 400 Gm. of this substance being stored here in a well nourished man.[17] This represents 20 to 25 per cent of the total amount of glycogen stored in the body, the voluntary muscles and the skin storing an equal or larger amount. Only liver glycogen, however, is directly transformable into dextrose and available for use by all body cells.[6] Newburgh and Conn[45] showed that disturbance of glycogen metabolism in the liver is the cause of diabetes in over-weight persons in the middle decades of life, comprising approximately 60 per cent of all persons with diabetes. A series of such patients, with true diabetic blood sugar curves following a dextrose tolerance test and with sugar in the urine, were found by Newburgh and Conn to regain a normal dextrose tolerance curve and to have urine continuously sugar free after a reduction in weight to normal for their age and height. Koehler and Sansum[34] have confirmed these findings, giving the dextrose intravenously to assure its absorption.

A further argument that the liver is primarily at fault in over-weight diabetic persons is given by Warren,[64] who made a detailed study of the pancreas in 484 diabetic persons. In 127, or 26 per cent, no alteration of any type could be demonstrated.

The implication of disturbed liver function as the important cause of diabetes in so large a group of subjects with this disease has met and will meet with vigorous opposition. But further evidence is not wanting. Meyer,[41] studying 100 diabetic patients in the Philadelphia General Hospital, found 28 per cent with laboratory evidence of liver dysfunction. Rabinowitch,[52] in an analysis of 3,000 blood samples from diabetic patients, found excess quantities of bilirubin in 27.4 per cent and an increased amount of urobilinogen in 27.5 per cent (assuming that detection in a dilution greater than 1:20 is abnormal). Jones and his associates,[28] in a study of 68 unselected diabetic patients, found abnormally high bile pigment elimination by the duodenum in 50, or 75 per cent. In 24, or 33 per cent, an associated enzyme disturbance of the lipolytic and proteolytic ferments was present. Acidosis produced a marked alteration of pancreatic enzyme activity and liver function. Improvement in these functions followed recovery from the acidosis.

Hepatomegaly occurred in 60 of Joslin's 1,000 diabetic children.[29] The edge of the liver was frequently in the pelvis. With improvement in the diabetes, the size of the liver decreased in 55 per cent.

Hemochromatosis, a rare disease, is characterized by diabetes, cirrhosis of the liver and pigmentation. The pigmentation in the skin and mucous membrane may be evident before the onset of diabetes.

Wilder[67] found an incidence of 28 per cent for cholelithiasis and of 34.5 per cent for gallbladder disease in 58 autopsies on diabetic subjects at the Mayo Clinic. Warren[64] found 31 per cent cholelithiasis and 36 per cent gallbladder disease in 453 autopsies on diabetic subjects in Boston. This is an obvious increase in these conditions as compared with statistics from routine postmortem examinations. The probability that chronic gallbladder disease in the diabetic initiates an acute pancreatitis is not important. However, inflammatory disease of the gallbladder may aggravate an existing diabetes. Diabetic patients, especially middle-aged women, who complain of digestive disorders should be studied with the possibility of chronic gallbladder disease in mind. Warren and Joslin recommended operative treatment of diabetic patients with gallbladder disease, with the object of sparing the liver and the pancreas additional damage.

The pituitary body apparently plays a significant role. With the solution of this problem, a new era may open in the management of diabetes.

The work of many experimenters has definitely demonstrated that special structures in the pancreas, the islands of Langerhans, elaborate the hormone insulin. Warren,[64] in a series of 487 specimens from his autopsy material, found no lesions in the pancreas or in other organs sufficient to explain the presence of diabetes in 127, or 26 per cent. Allen[1] stated many years ago: "Every anatomical hypothesis of diabetes still requires to be assisted by assuming the existence of a certain proportion of functional cases without known anatomical basis." Several explanations have been offered for this situation.

An absence of or clinical alteration in the acinar (external) secretion of the pancreas does not play an important role in the gastrointestinal manifestations of diabetes, although such changes occur. Bargan, Bollman and Kepler[3] treated 2 patients with true pancreatic insufficiency and steatorrhea. Pancreatic juice was given by mouth, with good results. The stools in such cases are bulky and offensive and have fat in large amounts. An occasional instance of intractable diarrhea, "diarrhea of diabetes," of undetermined origin is met. In this condition the stools are watery and numerous. The treatment is unsatisfactory and, owing to necessary diet changes, the diabetes is managed with difficulty.

As to the absence of free hydrochloric acid in the stomach in diabetes, especially in its relation to diarrhea, Bloomfield and Polland[5] reported varying statistics. The minimum incidence of anacidity reported was 25 per cent; the maximum, 40. The average for the reports reviewed approximated 37 per cent anacidity. Rathery and Ferroir,[54] with the use of histamine and fractional analyses, found hypochlorhydria in 31 per cent and anacidity in 19 per cent (total 50 per cent). When these groups are compared with control series of normal persons in approximately the same age groups, as has been done in the section on arthritis, the percentage of achylia is found to be about the same. The majority of compilers of statistics have attributed the occurrence of diarrhea in diabetic patients to an acholhydria or an achylia, and in part to the coarse diet on which diabetic patients are frequently placed. Diarrhea in diabetic patients is a distressing and at times a grave complication. It may lead to coma. Proper treatment of the diarrhea should be instituted at once. Failing a proper response, further serious complications must be sought for, such as amebiasis, ulcerative colitis and malignant growths of the intestinal tract.

Constipation is not a problem with diabetes. It can be properly managed with diet and, if necessary, with retention oil enemas. Laxatives are not needed.

Appendicitis in the diabetic is insidious in onset and never violent symptomatically. It must be kept in mind for patients for whom a differential diagnosis of abdominal abnormalities is indicated.

While certain evidence would suggest that cancer is more common with diabetes, this conclusion awaits the compilation of more data. Among 10,000 diabetic patients treated by Joslin,[30] 256 were found to have malignant growths of various types. The sites of cancer in order of frequency were as follows: pancreas, breast, uterus, stomach, liver, intestine, rectum, bladder, prostate and gallbladder. Among this group were 33 with carcinoma of the pancreas. In Warren's[64] series of 527 autopsies on persons who had diabetes, 47 with cancer were found. Ten, or 21 per cent, of these had cancer of the pancreas. From the data at hand, it is evident that cancer of the pancreas is seldom the cause of diabetes.

The evaluation of abdominal symptoms during coma and the differential diagnosis between coma and insulin shock are worthy of special emphasis. The term diabetic acidosis and coma are not synonymous. Acidosis develops over twenty-four to forty-eight hours as a rule. Bothe and Beardwood,[7] reviewing 1,260 admissions on a diabetic service, found 136 patients with acidosis, and of these 96, or 75 per cent, had nausea, vomiting, abdominal pain and tenderness. These symptoms were usually associated with fever and leukocytosis. Eighty-five per cent of these patients with abdominal symptoms had a leukocyte count varying from 11,000 to 44,000; 82 per cent had fever, the highest temperature being 104 F.

The onset of acidosis is attended by headache, malaise, nausea, vomiting and pains over various parts of the body, including the extremities. The clinical appearance of patients suffering from acidosis is often not unlike that of those with acute intestinal obstruction. They are toxic and markedly dehydrated and have abdominal distention, pain, nausea and vomiting.

Before any surgical procedure is undertaken, the acidosis should be treated. This can usually be controlled within three to six hours. Operation may be undertaken when the blood sugar level is two to three times normal, provided the carbon dioxide—combining power is not below 40 volumes per cent.

After their recovery from acidosis, Bothe and Beardwood's[7] patients were studied for lesions of the gastrointestinal and the genitourinary tract. No satisfactory explanation for the abdominal symptoms with acidosis was found.

An explanation of the cause of abdominal pain with acidosis has been offered by Walker.[63] A depletion of chloride in body tissues occurs with gastric tetany, heat cramps and diabetic acidosis. Abdominal symptoms in his one patient were relieved promptly by the administration of sodium chloride, and he suggested that the abdominal pain may be due to the low chloride content of the blood stream and body fluids.

The onset of acidosis, unless properly treated, often leads to coma. As the coma progresses, respirations become long and deep, and a fruity odor of the breath occurs, owing to saturation of the body with acetone bodies. The skin becomes cold and dry and the face flushed. The eyeballs are soft; the mouth and tongue dry, the latter with a dirty coating. The temperature is low, the pulse rapid and the blood pressure low.

It is occasionally necessary to differentiate between coma and insulin shock. The symptoms of the latter include hunger, nervousness, instability, sweating, numbness or tingling of the extremities, tongue or lips, double vision, headache, faintness, tremor, unsteady gait, rapid heart action, somnolence, unconsciousness and convulsions. The eyeballs are firm. Abdominal pain is absent. The blood sugar level in the presence of insulin shock is low; during coma it is high.

In summary, the gastrointestinal manifestations of diabetes are numerous and important. Dysfunction occurs in various portions of the tract, including the liver, pancreas, stomach and small and large bowel. Disease of the gallbladder and bile ducts may affect adversely the course of diabetes. Disturbed gastric secretion, pancreatic dysfunction and intestinal disturbance are likewise important. The evaluation of abdominal symptoms accompanying acidosis and coma warrants special emphasis. Insulin shock also causes gastrointestinal manifestations.

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CHAPTER XLVII

PELLAGRA, WITH SPECIAL REFERENCE TO THE ROLE OF THE DIGESTIVE TRACT

The entire subject of morbid states due to deficiency of vitamins of the B_2 group is in such an active state of flux that the present chapter must be considered more a progress note than a statement of established facts. Pellagra occurs mostly in the temperate and subtropical zones, but under somewhat varying circumstances. Endemic, annually relapsing pellagra is a major problem in the southeastern part of the United States and in Italy, Rumania and Egypt, in all of which maize is a large component of the diet of the poorer element of the population and carbohydrate makes up the major portion of food intake with relatively little supplementary aliment. Pellagra is seen in any locality in persons with severe chronic alcoholism, in occasional persons who have for some reason restricted their diet and in persons who have obstructive or fistulous lesions of the gastro-intestinal tract. Occasionally it is seen in persons who have eaten an apparently ample and well balanced diet. Because endemic pellagra occurs largely in areas where solar radiation is excessive, many attempts have been made to link exposure to sunlight with its incidence. The seasonal increase in pellagra in early spring and summer seems more likely the result of exhaustion of stored food factors during the winter months than of any effect of temperature. Particularly, there seems no good reason specifically to relate the dermatitis of pellagra to sunlight, since many different types of irritant may produce it and the whole syndrome may occur without exposure.

It has been known for more than twenty years that pellagra can be produced experimentally by prolonged administration of a diet high in carbohydrate and poor in vitamins of the B_2 group. Goldberger and his associates, in 1925 and 1926, showed that autoclaved yeast is curative in the majority of instances of mild pellagra. Patients with severe disease were cured with difficulty with yeast, and though there was marked general improvement in the pellagra situation, mortality rates, even in well conducted hospitals, continued high. Many paradoxes were encountered in attempts to establish theories of the cause of the disease and a satisfactory routine procedure for its treatment. The definitive etiology has been an active question particularly during the past five years, and even now many problems remain.

Symptoms.—The symptoms of pellagra are mainly referable to the digestive and nervous systems. Irritability, depression and easy fatigue may long precede any visible signs. Stupor and dementia also may be isolated symptoms. Paresthesia of the mouth and tongue, anorexia, nondescript digestive discomfort, constipation and, less often, diarrhea are frequent and may antedate any visible changes in the mouth or tongue. Vomiting, severe diarrhea often with incontinence, hyperpyrexia and delirium are common late symptoms in severe disease. Peripheral neuritis occurs occasionally in endemic pellagra and frequently in the "alcoholic" or "surgical" forms, and is probably due to concurrent vitamin B_1 deficiency.

Physical signs of pellagra are most variable. The complete syndrome includes dermatitis, stomatitis and glossitis, often proctitis and vaginitis. The signs of combined sclerosis or of peripheral neuritis may be present. Dermatitis is typically distributed over the forehead, malar eminences and nose, circumoral regions, neck, forearms and hands, genitalia and feet. Not infrequently the elbows and knees are involved. In acute pellagra the eruption is often vesicular, bullous or ulcerative. In chronic, recurring pellagra it is apt to be dry and pigmented; frequently there is follicular keratosis of the alae of the nose, the midportion of the forehead, the nasolabial folds and the chin. Dermatitis may seem to occur spontaneously; often it is apparently precipitated by exposure to sunlight, heat, any type of chemical irritant or friction. It is likely that genital lesions are the result of chemical irritation and that dermatitis of the elbows and knees results from friction. The complete series of skin changes may follow heavy exposure to x-rays. Stomatitis is usually ulcerative, involving the mucosa of the lips and buccal walls. Often there are fissures to the corners of the mouth, and gingivitis may be present. Glossitis is first evident as fiery redness of the tongue. Ulceration of the tip and edges follows the rapid atrophy of the lingual papillae, with the resulting bright red, slick tongue characteristic of this disease.

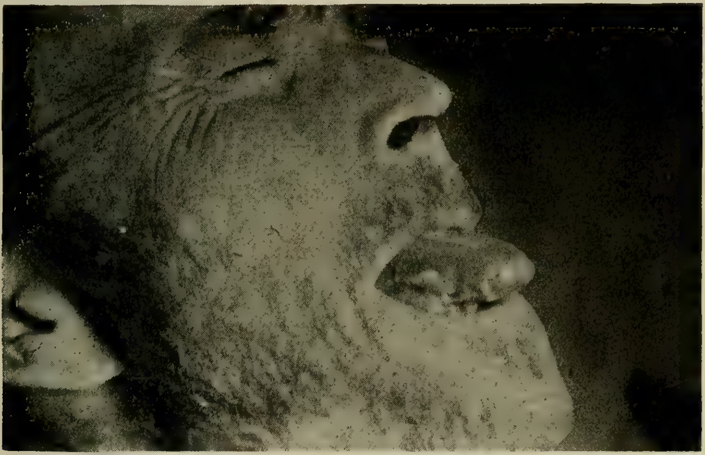

FIG. 178.—Atrophic ulcerated tongue in severe pellagra.

Secondary infection with Vincent's organisms or the thrush fungus is common. In chronic, recurrent disease faint brown pigmentation of the soft plate may be seen. Esophagitis is not infrequent and is associated with severe dysphagia, sometimes with the formation of a pseudomembrane.

Examination of the lungs and circulatory system is usually not significant, except that tachycardia and hypotension occur in a majority of patients. The abdomen in severe pellagra is frequently distended with gas and generally tender; the liver may be felt. Pigmentation of the rectal mucosa is common. Neurologic signs are exceedingly variable; there may be no abnormality or subacute combined sclerosis or peripheral neuritis.

The psychic pattern varies from mild or agitated depression to profound stupor or delirium.

Examination of the blood shows a high incidence of anemia of nutritional type. About 80 per cent of patients treated by my associates and me have shown simple hypochromic or hypochromic and microcytic anemia. Macrocytic anemia occurred in a small number (4.25 per cent), and occasionally true Addisonian anemia has been seen to follow frequent annual relapse of pellagra. Rarely patients with the clinical and hematologic picture of Addisonian anemia have failed to respond to parenteral liver therapy but have regained a normal blood picture under treatment with other substances curative for pellagra. Chemical examinations of the blood have not been significant. The gastric secretion of pellagrins is apt to be lacking in free hydrochloric acid and the enzymes. In our series of 660 cases achlorhydria was found in 77.3 per cent and subacidity in 17 per cent, while in only 5.7 per cent was there a normal amount of hydrochloric acid. The methods of examination varied with the progress of knowledge during twenty years, but the results following administration of histamine have not shown significant differences from those found with the Ewald and the alcohol test meal. In all cases the amount of secretion was apt to be small, and there was an excess of mucus. Routine examination of the urine of pellagrins has not been significant, though a small increase in the excretion of coproporphyrin can often be demonstrated. The stools have no significant characteristics. The cerebrospinal fluid shows no changes referable to the mental state of the patient or to neurologic signs.

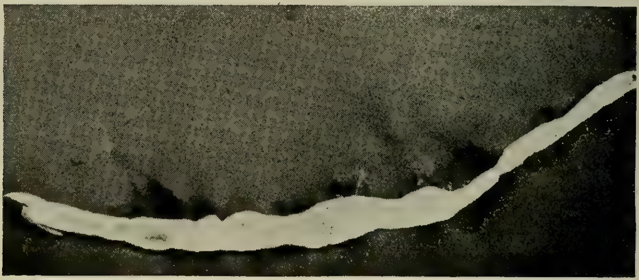

Fig. 179.—Fibrinous cast of esophagus vomited by pellagrin.

Pathology.—The pathologic picture of pellagra is well known.[3] Gross changes are seldom seen. The esophagus is frequently the site of a pseudomembrane. The heart is often small and may show "brown atrophy." The stomach may be dilated, with atrophy of the mucosa and smoothing out of the rugae. Occasionally there is a pseudomembranous gastritis. Congestion and superficial ulceration of the small and large bowel are frequently seen. The liver is regularly light in proportion to its size and is extremely fatty. Atypical changes in the adrenal glands have been described by some observers. Histologic findings are more important. Skin lesions show edema of the papillae, dilatation of the capillary bloodvessels and degeneration of the superficial collagen layer of the corium. Ulceration and secondary infection may cloud the picture. The oral lesions are not specific. The esophagus shows superficial ulceration with round cell infiltration of the deeper structures. The stomach has seldom been examined satisfactorily on account of rapid postmortem digestion of the mucosa. The small bowel is congested and occasionally shows superficial ulceration and leukocytic infiltration of the mucosa. The colon regularly is thickened, and many of the crypts of Lieberkühn show cystic dilatation. Ulceration and inflammation are frequent.

The liver is almost invariably extensively infiltrated with fat, often to such an extent that the normal architecture is obscured. There is no excess of pigment in the reticuloendothelial cells.

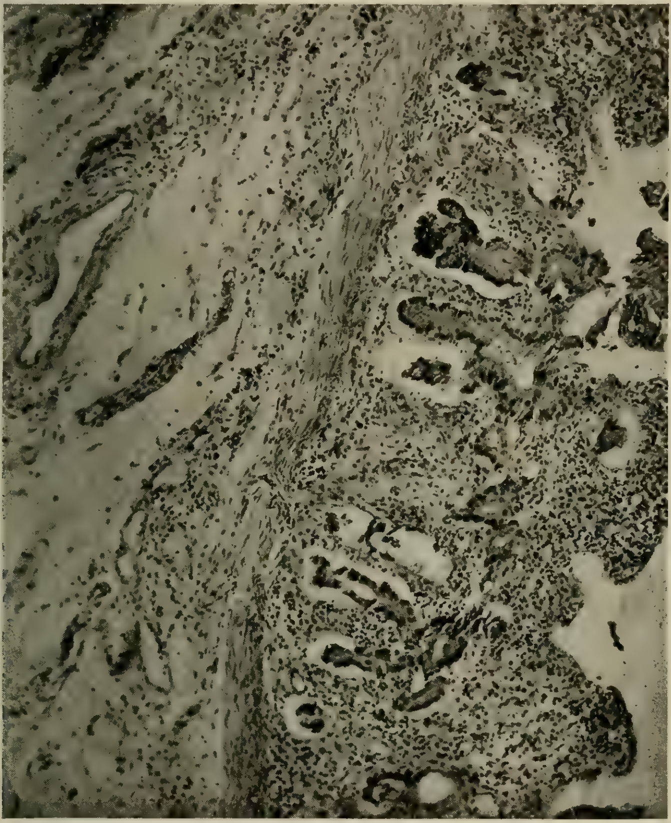

FIG. 180.—Mucosa of colon, showing superficial ulceration, dilatation of crypts and slight leukocytic infiltration; × 175.

Changes in the central nervous system are pronounced and widespread, involving the cortex of the brain, various tracts of the cord—usually the posterior and lateral columns—and the paravertebral ganglions. The large pyramidal cells of the cortex, particularly in the frontal lobes, show chromatolysis, fatty degeneration or accumulation, eccentric nuclei and axonal degeneration. These changes occur in irregularly distributed areas. In the lateral and posterior columns of the spinal cord there are irregular areas of myelin degeneration, disappearance of nerve cells and fibrous glial replacement, the picture being similar to, if not identical with, that of subacute combined sclerosis. None of these findings are specific for pellagra.

The functional abnormalities of the disease are perhaps more important than any anatomic changes. The acute nature of dermatitis in many instances suggests some relation to the swelling of nerve fibers with fragmentation of the axis cylinders, which has been described in the cutaneous nerves. Severe ulcerations in the mouth are usually due to secondary infection and resemble those occuring when local tissue resistance to bacterial invasion is lowered.

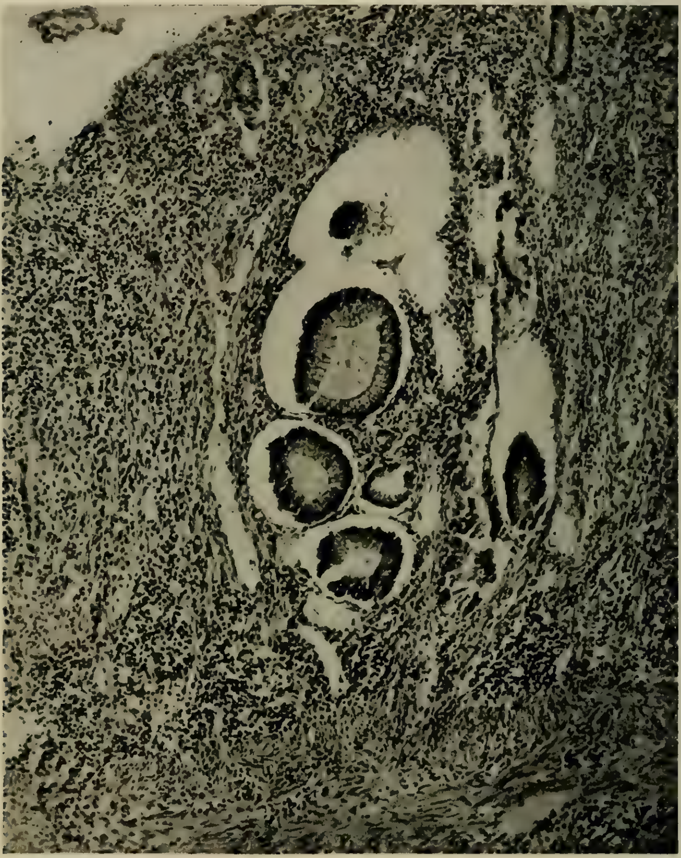

Fig. 181.—Mucosa of rectum, showing erosion, intense leukocytic infiltration and dilatation of glands; × 175.

Gastric achlorhydria seems to be a most significant sign of loss of gastric function, and my colleagues and I have attached great importance to this finding, particularly in view of its possible relation to combined sclerosis. This possibility has impressed many students of pellagra and caused much speculation regarding the possible etiologic similarity of pellagra and pernicious anemia. In our experience achlorhydria has been an adequate index of the severity of the disease and has seemed to have a direct relation to recovery and relapse. Unlike the achlorhydria of Addisonian anemia, that of pellagra frequently disappears under adequate treatment. The apparent importance of persistent achlorhydria is shown in our mortality rate. Of 446 patients whose gastric contents were adequately studied, 108 had some degree of free hydrochloric acid, and of these only 8 (7.4 per cent) died, while of the 338 with persistent achlorhydria, 66 (19.5 per cent) succumbed. Furthermore, recovery on a pellagra-producing diet occurred in 23 per cent of patients with persisting free acid but was seen in only 3 achlorhydric persons. Those patients who recover the ability to produce hydrochloric acid even after a long period seldom relapse, while those who remain achlorhydric during "cure" under specific therapy relapse almost without exception. The achlorhydric gastric juice of pellagrins shows a marked lack of pepsin and rennin, and Helmer, Fouts and Zerfas showed that mucous membranes of pellagrous stomachs obtained postmortem showed greatly reduced amounts of digestive ferments.

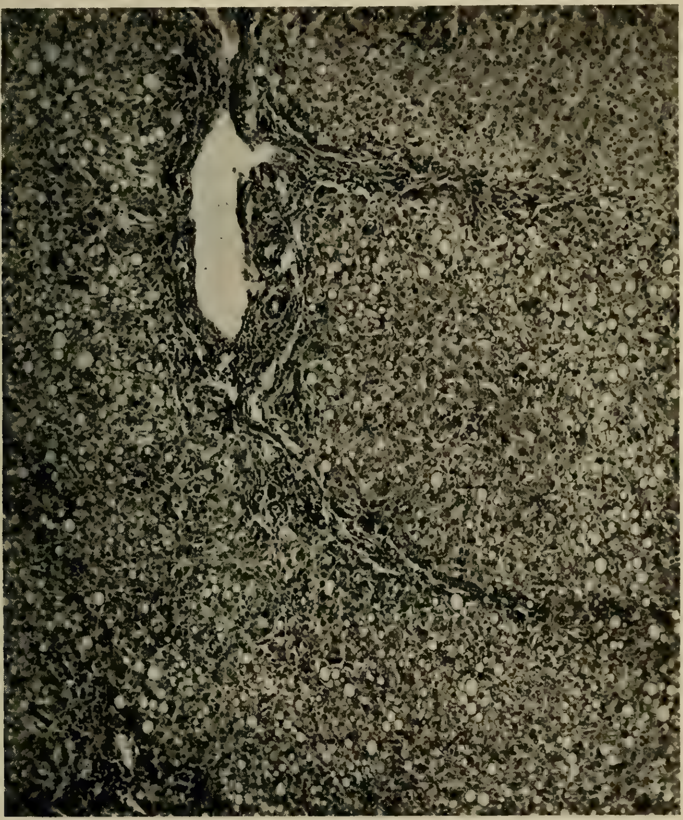

Fig 182.—Fatty infiltration of the liver in an untreated pellagrin; × 175.

The fatty liver of pellagra closely resembles that of pernicious anemia except that it does not contain an excess of pigment. It seems unlikely that function could remain unimpaired in the presence of such advanced degeneration. It is evident that the functional disturbance is of a different order from that in pernicious anemia, and it possibly represents simply a failure of storage. The triad of achlorhydria, fatty degeneration of the liver and frequently occurring disease of the central nervous system led to a consideration of the possibility that pellagra is a conditioned deficiency analogous to pernicious anemia and sprue. In empiric support of such a consideration were the demonstrated facts that liver and liver extract are curative for all three conditions and that certain yeast preparations are moderately effective in the treatment of pernicious anemia and sprue as well as of pellagra. It has also been known for long that pellagra as well as pernicious anemia may complicate extensive carcinoma of the stomach, gastric resection or chronic obstruction or fistulous disease of the bowel, pellagra being much the more frequent. It seemed important, too, to try to correlate a common endemic disease apparently resulting from faulty diet with a relatively uncommon condition usually considered a constitutional defect, both of which, however, are occasionally produced by an apparently similar mechanism. There seemed to be many possible lines of investigation. An intrinsic gastric deficiency analogous to that of pernicious anemia may be constitutional or factitious. The possible causes of factitious failure of gastric function are many. The taking of alcohol or other substances causing grave disturbance of normal gastric secretion, gross disease of the stomach or changes in the gastric mucosa secondary to prolonged vitamin deficiency are probably the most important. From the standpoint of extrinsic deficiency, hyperperistalsis with lack of normal absorption of food constituents, vomiting with loss of food and gastric juice and chronic starvation for vitamins all had to be taken into account. A related problem was the role of the liver in pellagra. Many of these matters were the objects of simultaneous investigation by other observers. Using the usual methods of control by diet known to be pellagra producing, my associates and I were able to show that normal human gastric juice, the gastric juice of pigs and fresh or desiccated extract of mucosa of pigs' stomachs are rapidly curative for pellagra. These results, which seem to indicate that there is an intrinsic gastric defect, were confirmed by Petri and his collaborators, who carried out similar and almost simultaneous experiments. In the meantime Spies and Payne and Salah had independently proved that the achlorhydric gastric juice of pellagrins contains the intrinsic factor of Castle; and we had shown that the extract of the fatty liver of an untreated pellagrin was rich in hemopoietic substances but entirely lacking in the pellagra-curative factor. The experiments seemed to indicate entirely different causes for pellagra and pernicious anemia.

At this juncture Elvehjem and his collaborators found that nicotinic acid is the specific black tongue—curative substance in liver extract. The immediate application of this discovery to human pellagra seemed to prove that nicotinic acid is the "P-P" factor of Goldberger. The effects of nicotinic acid are rapid and dramatic in most instances, comparable with those of frequent large doses of liver extract. The present status of the etiology of pellagra is largely based on observations made during the past eighteen months with the aid of nicotinic acid. In the light of present knowledge it would seem that the clinical syndrome is the result of nicotinic acid deficiency and that this deficiency may be due to inadequate intake, inadequate absorption or an undue requirement for or failure of utilization of the vitamin. These hypotheses fit well with clinical experience and may explain most of the paradoxes encountered in older theories. Diets productive of pellagra are known to be poor in nicotinic acid and its compounds, while yeast and liver are among the best natural sources. The influence of achlorhydria and gross gastrointestinal disease may be altogether confined to failure of absorption of nicotinic acid from ingested food, and fatty degeneration of the liver may become significant only by interfering with storage of nicotinamide. Petri, however, stated that nicotinic acid has no effect in preventing the development of "pig pellagra" in totally gastrectomized pigs and implied the necessity of the presence of functioning gastric mucosa for the utilization of nicotinic acid. This observation, if confirmed, may have great importance in supporting the hypothesis that gastric achlorhydria is of great significance. The specific requirement of the body for nicotinic acid seems to be for the synthesis of the dehydrogenases coenzyme and cozymase, which are essential to cellular respiratory processes. Riboflavin (vitamin B_2) also is a component of both substances. It seems probable that nicotinic acid, when administered therapeutically, has no effect except as a component of the coenzyme. Spies and his associates have recently demonstrated a deficiency of cozymase in the blood of pellagrins, and Kohn has demonstrated that coenzyme-like substances are increased by the administration of nicotinic acid. These observations raise further questions regarding the correlation of the gross and functional changes with biochemical phenomena. It would seem an inevitable conclusion that proper utilization of nicotinic acid in the sense of adequate synthesis of coenzyme is necessary for the symptomatic cure of pellagra. The mechanism of this synthesis is still obscure. The possible relation of riboflavin to the syndrome of human pellagra is not known.

Sebrell and Butler have pointed out that the "cheilitis" of "marginal stomatitis" so often seen in pellagra does not heal under nicotinic acid therapy, while riboflavin may produce rapid cure. My colleagues and I have been able to confirm this with certain reservations. The constant postmortem findings of fatty degeneration of the liver in human beings with pellagra and of riboflavin deficiency in dogs are suggestive of possible etiologic similarity, since dogs dying of black tongue produced by uncomplicated nicotinic acid deficiency do not have fatty liver.

Further interest has been aroused by the report of Corran and Green, who showed that flavoprotein catalysis depends on combination of the substance with reduced coenzyme and that oxygenation of the pyridine ring (nicotinamide) results in dissociation of the complex into oxidized coenzyme and the original flavoprotein. This suggests that flavin may be as necessary as nicotinic acid for the continuity of normal coenzyme activity.

The importance of nicotinic acid and possibly of riboflavin as components of coenzymes in human pellagra becomes more evident in acute pellagra occurring in patients maintained on dextrose and water, whether by necessity after surgical operation or by intent in the experimental production of relapse. Such patients, receiving nothing but pure carbohydrate and with no vitamin intake, use up coenzyme and vitamin B_1 at a very rapid rate and may show the complete syndrome of pellagra on the fourth or fifth day, with polyneuritis soon afterward. Frequently, but not constantly, achlorhydria develops. The mechanism of the development of endemic pellagra in persons on a diet constantly high in carbohydrate and low in B vitamins becomes fairly clear, and it is possible that many clinical problems of the disease may soon be solved. It is to be kept in mind that a diet which produces endemic pellagra is poor in most of the vitamins and that the disease is produced only after a long period of malnutrition, so that in most instances it amounts to a multiple avitaminosis. The probable but as yet unproved hypothesis of the synergistic action of vitamins is a question of great importance in the definitive etiology of pellagra and may have much bearing on optimal methods of treatment.

For the present, pellagra may be considered a syndrome resulting from prolonged deprivation of nicotinic acid and possibly other vitamins of the B_2 group. This deprivation may be brought about not only by deficient intake of such substances but by a diet almost exclusively carbohydrate, with resulting increase in the requirement for nicotinic acid. Possibly as a primary result of avitaminosis there is loss of gastric function, which further hinders absorption and possible utilization of vitamins; this loss of gastric function may be, and indeed often is, irreversible, so that permanent conditioning results. There is experimental evidence to suggest that the utilization of nicotinic acid is in some way determined by the functioning gastric mucosa. Changes in the liver are possibly secondary, but may interfere with synthesis of coenzyme or storage of vitamins. Lesions of the central nervous system are probably also secondary.

Treatment.—The treatment of pellagra has been much simplified by the introduction of nicotinic acid, though it must be remembered that urgently ill patients still require various active therapeutic measures. Rest is most important even for mild pellagra, because it immediately reduces the metabolic requirements. In the past many patients have recovered simply from rest in bed. For mild endemic pellagra, rest, an adequate high caloric, high protein diet and the administration of 50 to 150 mg. of nicotinic acid a day may be all that is necessary for rapid improvement. For serious illness a much more complicated regimen is required. Vomiting and diarrhea frequently produce extreme grades of dehydration and ketosis, so that administration of fluids subcutaneously and intravenously is necessary. Large amounts of salt and dextrose solutions, preferably "buffered with insulin" are necessary. It is important, however, not to waterlog the patient. Feeding is most important and should be carried out through an indwelling tube when the patient is stuporous or uncoöperative. The liquid diet of Spies, Chinn and McLester is adequate. For patients who are able to coöperate, the soft or solid curative diets suggested by the same authors are most useful. Painful stomatitis and glossitis often interfere with eating. For these, the use of mild alkaline mouth washes and touching of ulcers with 1 per cent chromic acid or 5 per cent silver nitrate are usually adequate. Severe diarrhea requires the administration of opium, either as morphia hypodermically in amounts sufficient to control hyperperistalsis or as tincture of opium in doses of 10 to 20 minims mixed with bismuth subnitrate in doses of 1 drachm. Such a mixture can be given every two or three hours until diarrhea stops. Dermatitis may be so mild as to require no treatment. For simple erythema or the dry pigmented dermatitis of chronic pellagra calamine lotion or zinc oxide ointment suffices. For severe, bullous and ulcerative types of dermatitis soaks of 1:5,000 potassium permanganate are most useful in treating the hands and feet. Perineal lesions are best treated with 1 per cent gentian violet or 2 per cent tannic acid painted on several times a day. Tannic acid also is useful for bullous and ulcerative lesions of the hands and elbows. The elbows, knees and sacral regions should be protected against pressure and friction. Nicotinic acid is probably the substance of choice in the treatment of all severe pellagra. The amount needed for cure is extremely variable and considerably influenced by the method of administration. I have found that 600 mg. of nicotinic acid given by mouth in doses of 100 mg. six times a day will produce dramatic cure in a great majority of instances, though some patients may require as much as 1,000 or even 1,800 mg. during the first twenty-four hours. Many patients do not require such large amounts, and my usual method is to begin treatment with 300 mg. daily, in six doses of 50 mg. Administered intravenously as sodium nicotinate, the amount required for cure varies from 100 to 400 mg. It is my custom to give 100 mg. at a dose in a volume of 200 cubic centimeters. Occasional patients require prolonged administration of the vitamin. Results, as mentioned before, are usually dramatic. Glossitis, stomatitis and diarrhea are cured in thirty-six to forty-eight hours. Mental symptoms may disappear after the first large dose of nicotinic acid or may persist, necessitating prolonged treatment after other manifestations have cleared. Dermatitis heals more slowly than with yeast or liver, and in practice it is perhaps advisable to use one of these substances as an adjunct to nicotinic acid. For the maintenance of pellagra patients who have recovered from their acute symptoms an adequate diet is most important. With this, nicotinic acid may be required in amounts of 50 to 600 mg. a day, and I have found it advisable to include from 30 to 45 Gm. of yeast routinely. The anemia of pellagra usually responds rapidly to any form of iron but does not seem to be materially influenced by added liver. The response of gastric secretion, I feel, is most important in determining the maintenance treatment of pellagra, for patients in whom no regeneration of acid occurs are almost certain to relapse unless treatment is kept up over an indefinite period.

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